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Gunjan L. Shah, … , Genovefa A. Papanicolaou, Miguel-Angel Perales

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BACKGROUND. Understanding outcomes and immunologic characteristics of cellular therapy recipients with SARS-CoV-2 is critical to performing these potentially life-saving therapies in the COVID-19 era. In this study of recipients of allogeneic (Allo) and autologous (Auto) hematopoietic cell transplant and CD19-directed chimeric antigen receptor T cell therapy (CAR-T) at Memorial Sloan Kettering Cancer Center, we aimed to identify clinical variables associated with COVID-19 severity and assess lymphocyte populations.

METHODS. We retrospectively investigated patients diagnosed between March 15th and May 7th, 2020. In a subset of patients, lymphocyte immunophenotyping, quantitative real-time PCR from nasopharyngeal swabs, and SARS-CoV-2 antibody status were available.

RESULTS. We identified 77 SARS-CoV-2 + cellular therapy recipients (Allo = 35, Auto = 37, CAR-T = 5; median time from cellular therapy 782 days (IQR 354,1611). Overall survival at 30 days was 78%. Clinical variables significantly associated with the composite endpoint of non-rebreather or higher oxygen requirement and death (n events = 25/77) included number of co-morbidities (HR 5.41, $P = 0.004$), infiltrates (HR 3.08, $P = 0.032$), and neutropenia (HR 1.15, $P = 0.04$). Worsening graft-versus-host-disease was not identified among Allo subjects. Immune profiling revealed reductions and rapid recovery in lymphocyte populations across lymphocyte subsets. Antibody responses were seen in a subset of patients.

CONCLUSION. In this series of Allo, Auto, and CAR-T recipients, we report overall favorable clinical […]

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Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation

Gunjan L. Shah*[1,2], Susan DeWolf*[1], Yeon Joo Lee[2,3], Roni Tamari[1], Parastoo B. Dahi[1], Jessica A. Lavery[4], Josel Ruiz[1], Sean M. Devlin[4], Christina Cho[1,2], Jonathan U. Peled[1,2], Ioannis Politikos[1,2], Michael Scordo[1,2], N. Esther Babady[5], Tania Jain[1], Santosha Vardhana[2,7], Anthony Daniyan[2,8], Craig S. Sauter[1,2], Juliet N. Barker[1,2], Sergio A. Giralt[1,2], Cheryl Goss[9], Peter Maslak[10], Tobias M. Hohl[2,3], Mini Kamboj[2,3], Lakshmi Ramanathan[6], Marcel R.M. van den Brink[1,2], Esperanza Papadopoulos[1,2], Genovefa Papanicolaou[2,3], Miguel-Angel Perales[1,2]

*Contributed equally to manuscript

[1]Adult BMT Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[2]Department of Medicine, Weill Cornell Medical College, New York, NY

[3]Infectious Disease Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[4]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[5]Clinical Microbiology Service, Department of Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[6]Clinical Chemistry Service, Department of Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[7]Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[8]Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[9]Transfusion Medicine Service, Department of Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[10]Cellular Immunology Laboratory, Department of Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Corresponding Author:

Gunjan L. Shah

1275 York Avenue

New York, NY 10065

212-639-2000

shahg@mskcc.org

Conflicts of Interest:

SDW, RT, JAL, JR, SMD, CC, EB, AD, CG, PM, MK, LVR, EP, GP report no conflicts of interest. GLS reports research funding from Janssen and Amgen. YJL receives support for the conduct of industry sponsored trials from Astellas Pharma and Ansun BioPharma. PD served on an advisory board for Kite. JUP reports research funding, intellectual property fees, and travel reimbursement from Seres Therapeutics and consulting fees from DaVolterra. IP reports research funding from Merck and serves on a Data and Safety Monitoring Board for ExCellThera. MS has served as a paid consultant for McKinsey & Company, Angiocrine Bioscience, Inc., and Omeros Corporation. He reports research funding from Angiocrine Bioscience, Inc. He has served on an ad hoc advisory board for Kite – A Gilead Company.TJ reports consultancy honoraria from Takeda Oncology and has served on an advisory board for CareDx. SAV reported personal fees from Immunai and personal fees from ADC Therapeutics outside the submitted work; in addition, SAV had a patent to PCT/US19/27610 pending. CSS has served as a paid consultant on advisory boards for: Juno Therapeutics, Sanofi-Genzyme, Spectrum Pharmaceuticals, Novartis, Genmab, Precision Biosciences, Kite/a Gilead Company, Celgene, Gamida Cell and GSK. He reports research funding from Juno Therapeutics, Celgene, Precision Biosciences and Sanofi-Genzyme. JNB reports research funding from Angiocrine Bioscience, Gamida Cell, and Merck. SAG has consulted for and received research funding from Amgen, Actinium, Celgene, Johnson & Johnson, BMS, Sanofi, Pfizer, and Takeda; has consulted for Jazz Pharmaceuticals, GSK, Novartis, Kite, and Spectrum Pharmaceuticals; and has received research funding from Miltenyi. TMH has participated in scientific advisory boards for Merck & Co, Inc. and Partner Therapeutics. MVDB has received research support from Seres Therapeutics; has consulted, received honorarium from or participated in advisory boards for Seres Therapeutics, Forty-Seven

Inc., Magenta, Juno Therapeutics, Rheos, WindMIL Therapeutics, Novartis, Evelo, Jazz Pharmaceuticals, Therakos, Amgen, Magenta Therapeutics, Merck & Co, Inc., Acute Leukemia Forum (ALF) and DKMS Medical Council (Board); has IP Licensing with Seres Therapeutics, Juno Therapeutics, and stock options from Smart Immune. MAP has served on advisory boards for MolMed, NexImmune, Medigene, and Servier; has received honoraria and served on advisory boards for Abbvie, Bellicum, Bristol-Meyers Squibb, Nektar Therapeutics, Novartis, Omeros, and Takeda; has consulted for and received honoraria from Merck; and has received research funding from Kite/Gilead, Incyte, and Miltenyi.

Abstract

Background: Understanding outcomes and immunologic characteristics of cellular therapy recipients with SARS-CoV-2 is critical to performing these potentially life-saving therapies in the COVID-19 era. In this study of recipients of allogeneic (Allo) and autologous (Auto) hematopoietic cell transplant and CD19-directed chimeric antigen receptor T cell therapy (CAR-T) at Memorial Sloan Kettering Cancer Center, we aimed to identify clinical variables associated with COVID-19 severity and assess lymphocyte populations.

Methods: We retrospectively investigated patients diagnosed between March 15th and May 7th, 2020. In a subset of patients, lymphocyte immunophenotyping, quantitative real-time PCR from nasopharyngeal swabs, and SARS-CoV-2 antibody status were available.

Results: We identified 77 SARS-CoV-2 + cellular therapy recipients (Allo = 35, Auto = 37, CAR-T = 5; median time from cellular therapy 782 days (IQR 354,1611). Overall survival at 30 days was 78%. Clinical variables significantly associated with the composite endpoint of non-rebreather or higher oxygen requirement and death (n events = 25/77) included number of co-morbidities (HR 5.41, p=0.004), infiltrates (HR 3.08, p=0.032), and neutropenia (HR 1.15, p=0.04). Worsening graft-versus-host-disease was not identified among Allo subjects. Immune profiling revealed reductions and rapid recovery in lymphocyte populations across lymphocyte subsets. Antibody responses were seen in a subset of patients.

Conclusion: In this series of Allo, Auto, and CAR-T recipients, we report overall favorable clinical outcomes for COVID-19 patients without active malignancy and provide preliminary

insights into the lymphocyte populations that are key for the anti-viral response and immune reconstitution.

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Introduction:

As of June 2, 2020, there were over 1.8 million confirmed cases of COVID-19 caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in the United States, with more than 16,000 deaths in New York City (1). The vulnerability of patients with significant comorbidities became evident early in this public health crisis and cancer patients were considered potentially one of the most at-risk groups due their immunocompromised state related to underlying malignancy and associated treatments, but these studies included primarily patient with solid tumors (2). More recent studies focused on patients with hematologic malignancy confirmed that previously identified risk factors for disease severity also held true for these patients (3–7).

T cells are the key mediators of antiviral immune responses and studies of lymphocytes in COVID-19 patients are beginning to emerge (8). Lymphopenia is the hallmark of severe COVID-19 presentations (9), and small series suggest this affects T cells, B cells, and NK cells (10–13). Recipients of cellular therapies, including allogeneic hematopoietic cell transplantation (Allo), autologous hematopoietic cell transplantation (Auto), and CD19 directed chimeric antigen receptor T cell therapy (CAR T), are a unique population of patients with hematologic malignancies due to their immune dysregulation and prolonged timeline for immune reconstitution.

In this study, we sought to characterize the clinical course of patients with hematologic malignancies who previously received Allo, Auto, or CAR T and evaluate changes in lymphocyte and T cell subsets during SARS-CoV-2 infection at Memorial Sloan Kettering

Cancer Center (MSKCC). With need to conserve hospital resources and concern for patient safety, centers performed only emergent transplants with guidelines suggesting delaying elective transplants and cellular therapies during the pandemic. We describe potential risk factors for severe disease in this immunocompromised population to allow for mitigation and treatment of COVID-19 and to guide transplant centers as they resume these potentially life-saving treatments based on local conditions.

Results:

Demographics, Disease, and Treatment Characteristics

Between March 11 and May 7, 2020, 77 patients (Allo n= 35, Auto n=37, CAR T n=5) met criteria for diagnosis of COVID-19, with median follow-up in surviving patients of 23 days [interquartile range (IQR) 14, 35]. The median age at COVID-19 diagnosis was 62 (range 25-78), with 17% over age 70 and 64% male (Table 1). Median time from most recent cell therapy was 782 days (IQR 354,1611). All CAR T patients received FDA-approved commercial products with 80% axicabtagene ciloleucel. At time of COVID-19 diagnosis, 17% of Allo patients had active graft-versus-host disease (GVHD), which did not worsen during their course. No patients had a new diagnosis of GVHD during their COVID-19 treatment.

Most patients had never smoked (66%) or vaped (96%). The median body mass index (BMI) was 27.4 kg/m^2 (IQR 24.1, 30.6). At the time of COVID-19 diagnosis, 22% of patients had 2 comorbidities when considering hypertension, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, human immunodeficiency virus (HIV), and chronic kidney disease, while 44% had none of these issues (Figure 1). Patients were on aspirin (26%); immunomodulatory agents (lenalidomide/pomalidomide, 23%); GVHD immunosuppressive agents (tacrolimus, cyclosporine, mycophenolate mofetil, and/or ruxolitinib, 18%); steroids (13%); angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers (7%); and anticoagulation medications (5%). No patients were on BTK inhibitors at the time of COVID-19 diagnosis. Thirteen percent received intravenous immunoglobulin within 3 months prior to COVID-19 diagnosis.

Regarding the status of the hematologic malignancy, 25% had relapse or progression of disease after Allo, Auto, or CAR T. At the time of COVID-19 diagnosis, the most recent disease status was: in remission not on treatment, in remission on consolidation or maintenance treatment, stable disease but not in remission, or relapsed/refractory disease in 48%, 22%, 14%, and 16%, respectively. As most patients were in remission or on maintenance, 62% did not have any changes in treatment plan at time of diagnosis, but treatment was delayed or permanently discontinued in 31% and 3%, respectively.

Symptoms and Clinical Course

Clinical presentation

Seventy-four patients had a positive nasopharyngeal swab (NPS) for SARS-CoV-2 RNA (25% tested outside MSK), with 3 patients having presumed disease, and 45% having a known positive contact. Symptoms at diagnosis included cough (65%), fever (58%), fatigue (39%), shortness of breath (30%), myalgias (27%), headache (16%), nausea/vomiting (10%), anosmia (9%), rhinorrhea (8%), confusion (8%), diarrhea (7%), and diaphoresis (4%). At time of initial positive NPS, oxygen saturation was checked in 43 patients (56%) and was below 90% in 21%. Fifty percent of patients had imaging done with 64% of those studies revealing an infiltrate.

Laboratory data

Laboratory tests were performed in 65% of patients at the time of COVID-19 diagnosis. The median neutrophil count was 3.2k/mcL (IQR 1.7,5), 3.4 (IQR 1.9,6.2), 2.8 (IQR 1.5, 4.4), and 3.6 (IQR 2.9, 4.3) for all patients, Allo, Auto, and CAR T, respectively. Lymphopenia was common with the median absolute lymphocyte count (ALC) 0.9 k/mcL (IQR 0.5, 1.5), 0.9 (IQR

0.6, 2), 0.9 (IQR 0.5, 1.3), 0.3 (IQR 0.3, 0.4) for all patients, Allo, Auto, and CAR T, respectively. Overall, the median neutrophil/lymphocyte ratio was 3.55 (range 0.67-60). Renal and hepatic function was mostly not impacted. Additional laboratory values at time of positive NPS, time of admission, and maximums throughout COVID-19 course are in Supplemental Table 1. Median maximum values of inflammatory markers included ferritin 1396ng/mL (IQR 277, 4305, n=30), c-reactive protein 16.9mg/dL (IQR 10.1, 26.4, n=31), and interleukin-6 (IL-6, pre-tocilizumab in those that received it) 93.5pg/mL (IQR 34.3, 231, n=30).

Cycle threshold (Ct) is a semiquantitative estimate of the viral load on a NPS and was available for 68%, with median Ct for N2 (a region of the nucleocapsid gene) on diagnostic NPS 22.65 (IQR 19.53,29.18). Routine swabbing until negativity was not done, but of the 58% with serial testing, a median of 2 NPS (IQR 2,3.5) were done with 52% negative on most recent NPS and median time to negativity of 28 days (IQR 22, 35). For those with the most recent NPS still positive, median time from initial positive to most recent positive was 44 days (IQR 23, 57). Ct values trended upward overtime in most but not all patients during the study period (Figure 2).

COVID-19 directed treatments

COVID-19 directed treatment was given to 47% of patients overall with 1/3 of patients receiving treatment on a clinical trial. The most common treatments included hydroxychloroquine (32%) started a median of 1 day after COVID-19 diagnosis (IQR 1-2), azithromycin (25%) at 1 day (IQR 0-2), methylprednisolone (18%) at 6 days (IQR 4-11), convalescent plasma (16%) at 10 days (IQR 5-15), intravenous immunoglobulin (6%) at 6 days (IQR 2-13), tocilizumab (10%) at 8 days (IQR 5-13), remdesivir (4%) at 14 days (IQR 10-15), n-acetylcystine (3%) at 29 days

(IQR 29-30), siltuximab (n=1) at 7 days, and anakinra (n=1) at 9 days (Supplemental Table 2). Overall, 15 patients had IL-6 levels drawn and 8 received tocilizumab or siltuximab. The median IL-6 level pre-IL-6 directed therapy was 176.7 pg/mL (range 49.5-1578.4). While patients may have had an inflammatory response similar to hemophagocytic lymphohistiocytosis (HLH), no other HLH directed treatments were administered. In addition, 48% received antibacterial coverage for potential superimposed bacterial infection.

Clinical course and outcomes

Forty-four percent of patients required admission with 24/34 admitted on the same day as the positive NPS, while an additional 8% were already admitted for treatment of their malignancy at the time of positive NPS. Median length of stay for the initial hospitalization was 8 days (IQR 5-18). At last follow-up, 24 patients (71%) were discharged with two readmitted during the follow-up time. Secondary infections were formally documented in 10 patients (with some having multiple infections) and included bacteremia (n=3), fungal pneumonia (n=3), urinary tract infection (n=2), clostridium difficile diarrhea (n=2), bacterial pneumonia (n=1), EBV reactivation (n=1). Prophylaxis for venous thrombosis was given in patients with an adequate platelet count (24/34). Two patients developed thromboses with one having thrombocytopenia precluding anticoagulation and one having a prior history of venous thrombosis who developed a catheter associated thrombosis when prophylaxis was discontinued due to thrombocytopenia. No cerebrovascular accidents were seen. No prior dialysis-naïve patients required dialysis. Fifty seven percent (44/77) of patients did not require supplemental oxygen, while 32% required a non-rebreather (NRB) or higher level of supplementation (Figure 3A). Nine (25% of those admitted) required intubation with 3 patients extubated, 5 dying while intubated, and 1 remaining

on the ventilator. The median time to extubation or death in the intubated patients was 12 days (IQR 8-22). Ten patients required pressor support in the intensive care unit. Code status was changed to do not resuscitate on 13 admitted patients with 5 changed after intubation. Overall, 48%, 26%, and 22% had mild, moderate, or severe COVID with 12/17 patients with severe disease dying (Figure 3B). The median time from diagnosis to resolution of symptoms was 14 days (IQR 10-20). Of the 14 patients who died, 8 (57%) had active disease at COVID-19 diagnosis and 4 were within 1 year of cellular therapy (Figure 4). Overall survival at 30 days was 78% (95% CI 68-91%), with 73% (CI 57-94%), 87% (73-100%), and 60% (29-100%) of Allo, Auto, and CAR T patients alive, respectively (Figure 5).

Factors associated with Disease Severity

In an effort to not under-categorize severity, we created a composite endpoint of requiring a NRB or higher oxygen or death at a lower level of oxygen as there were patients who did not get intubated or were not transferred to the intensive care unit based on goals of care discussions with the patient, their family, and the clinical team taking into account their COVID course and the status of their underlying malignancy. Univariable analysis for this composite endpoint was significant for number of comorbidities (Hazard ratio (HR) for $\geq$2 vs none 5.41 (95% CI 1.84-15.9, p=0.004), presence of infiltrates on initial imaging (HR 3.08, 95% CI 1-9.44, p=0.032), and neutropenia (HR 1.15, 95% CI 1.02-1.29, p=0.04) (Table 2). Having more than 2 comorbidities (p=0.002) and an active hematologic malignancy (p = 0.02) predicted for increased disease severity by univariable analysis (Supplemental Table 3).

Evaluation of lymphocyte subsets in SARS-CoV-2+ BMT patients

Monitoring of immune reconstitution post-transplant is standard clinical practice at MSKCC, including lymphocyte subsets (CD4+ T cells, CD8+ T cells, CD19+ B cells, CD56+ CD16+ NK cells, and CD3+ CD56+ CD16+ NKT cells) and, in some patients, additional T cell populations including naive (CD45RA+ CCR7+), central memory (CD45RA- CCR7+), effector memory (CD45RA- CCR7-), and effector memory CD45RA+ or TEMRA cells (CD45RA+CCR7-) (14,15). During the study period, immune subset analyses were performed in 32 out of the 77 patients, including 17 Allo, 12 Auto, and 3 CAR T. We selected 25 patients within one week of any positive SARS-CoV-2 PCR test for further analysis (Table 3, Figure S1).

Infection with SARS-CoV-2 is related to a reduction in lymphocyte populations

Because transplant patients are a uniquely heterogeneous population with regards to the circulating immune cells affected by the type of transplant, state of immune reconstitution, immunosuppression regimen, GVHD, and disease status, we used pre-COVID-19 immunologic profiling available in 12/25 patients as an internal control. Consistent with prior studies, a reduction from pre-COVID baseline in ALC was observed in this cohort, except for one patient whose prior immune subsets were performed just after completing conditioning for CAR-T therapy. The reduction in lymphocytes affected all subsets for most patients, particularly CD4 and CD8 T cells; in some patients B cells and NK cells remained stable or increased slightly (Figure 6A). The CD4:CD8 ratio varied widely across patients with a trend toward a relative increase in CD4 T cells (Figure S2A). For Allo recipients within two years post-transplant, we further compared lymphocyte subset data with the expected post-HCT immunologic

reconstitution from available historical control cohorts (Figure 6B, Figure S3), highlighting how COVID-19 is associated with lower lymphocyte counts, particularly in the T cell compartment.

Detailed T cell phenotyping was available in 18/25 patients with COVID-19 revealed that CD4 cells were predominantly effector memory cells while CD8s had a TEMRA phenotype (CCR7-CD45RA+); naïve cells were similar in both CD4s and CD8s (Figure S4). Six patients had prior T cell subset profiling data available within one year of COVID-19 (Figure S5). There was a trend toward an increase in percentage of CD8+, but not CD4+, TEMRA cells during the COVID-19 window; however, this was not seen by absolute counts.

Patients can develop Immunoglobulin G (IgG) antibody responses to SARS-COV-2 despite lymphopenia

During the time of our study, a SAR-CoV-2 antibody test became available. Thirty-eight patients (49%) had antibody testing done at a median of 37 days after diagnosis (IQR 28, 48) with 66% of those developing antibodies, including 5/10 patients on immunosuppressive medications. In seven patients who received convalescent plasma, antibody testing at least two weeks after infusion was negative in 6. For the patient with antibodies, repeat testing one week later remained positive and is thought to be a true positive response. In a subset of 8 patients who had not received convalescent plasma, but had a positive antibody and immune profiling performed within the COVID period, six patients had circulating absolute B cells counts under 100 cells/ucl, including two with no detectable circulating B cells but measurable IgG levels (Figure S6).

Lymphopenia with COVID-19 does not appear to impair immune reconstitution in all BMT patients

We next sought to investigate the persistence of lymphopenia associated with COVID-19. Figure 7 illustrates the trajectory lymphocyte populations before, during, and in recovery from COVID-19 in a patient with AML disease who received a transplant from a haploidentical donor, highlighting how lymphocytes began to recover, even though the patient did not yet have a detectable SARS-CoV-2 antibody. Available data from other patients had an overall similar trajectory, other than one patient with a fatal infection combined with underlying MDS (Figure S7).

Discussion:

We present the largest series of COVID-19 outcomes for patients who have received cellular therapies including Allo, Auto, and CAR T. The percentage of patients with underlying comorbidities is similar to what would be expected post-transplant (16). Overall, almost half of the patients were monitored and recovered entirely as outpatients without any outpatient deaths. Treatments varied throughout the time period due to rapid iterative changes in clinical management algorithms. Documented secondary infections were uncommon, including in those patients who received IL-6 directed therapies, similar to CAR-T patients treated for with tocilizumab for cytokine release syndrome (17,18). Interestingly, time from cellular therapy and many previously reported risk factors for disease severity were not significant in our analysis, though analyses were limited by the small number of events. Immune alterations, most predominantly lymphopenia, were seen, but it appeared that improvements in lymphocyte counts occurred within a short period of time after resolution of symptoms.

The clinical presentation and overall course of COVID-19 was similar to those from other large cohorts from academic centers in New York (19,20), from cancer patients (2,21–23), particularly those with hematologic malignancies (7,24–27) and solid organ transplant patients on immunosuppression (28). Symptoms at presentation were common across all cohorts and included fevers, cough, and shortness of breath. The presence of infiltrates at time of diagnosis and requirement for oxygen supplementation portended worse outcomes. In a cohort of solid organ transplant patients treated in the New York Presbyterian system, the distribution of disease severity appears to be increased when on immunosuppression compared to our population (majority not on immunosuppression), with 24%, 46%, and 30% vs 48%, 26%, and 22% having

mild, moderate, and severe disease, respectively. While our median follow-up was 23 days, the interquartile range for resolution of symptoms was 10-20 days, and there were few patients with ongoing symptoms at the time of our data cutoff.

In our cohort, the overall mortality rate was 41% in hospitalized patients, but this was largely driven by patients with active malignancy, especially relapsed leukemia in whom the goals of care were impacted both by COVID-19 severity and the decision to forgo anti-cancer treatment during an active infection. For the patients with hematologic malignancies treated in the Montefiore Health system, the case fatality rate was 37% (20/54) (22). In our cohort of cellular therapy recipients without active malignancy, the death rate was 21%, which matched the reported mortality of patients hospitalized with COVID-19 in New York (20).

Interestingly, outcomes in our study were not different based on the type of hematologic malignancy. A large portion of patients had Auto for multiple myeloma, and our results are similar to the Mt. Sinai cohort, in which 22/54 (41%) had an Auto previously (24). Exposure to a person infected with SARS-CoV2 was a significant risk factor for developing COVID-19 in a cohort of chronic myeloid leukemia patients treated with tyrosine kinase inhibitors (26). In our study, 45% of patients had a known exposure outside of the medical system. Therefore, while limited clinic visits and telemedicine interactions with the medical system are important, social distancing, use of personal protective equipment, and infection control even at home may be needed to protect patients with hematologic malignancies from contracting SARS-CoV-2 and presents an obstacle to address during a potential second wave.

GI symptoms in COVID-19 present a particular challenge in Allo patients because it may be difficult to differentiate from GVHD. In our cohort, for those patients on immunosuppression, their GVHD did not worsen. Importantly, though we would be concerned for an infection triggering GVHD, no Allo patients had new GVHD arise during their COVID-19 course, with the caveat of a relatively short follow-up window.

Understanding the adaptive immune response in COVID-19 BMT patients is critical because of the immunocompromised nature of these patients and well-established role of viral infection in modulating immune reconstitution following transplantation (29–33). Lymphopenia is a common feature of SARS-CoV-2 infection, particularly in severe cases. Our data is consistent with that of others identifying that SARS-CoV-2 infection does not specifically target an immune subset but rather leads to marked reduction across lymphocyte populations (10–13). Phenotypic evaluation of 20 non-HCT patients who recovered revealed a slight increase in the percentage of CD3 T cells with a reduction in CD19 B cells compared to healthy controls (34); however, pre-COVID-19 or mid-COVID-19 lymphocyte characterization was not available. A strength of our study is that we were able to compare longitudinal immune subsets before and after SARS-CoV-2 infection. We demonstrate that although some of our patients were less than a year post-transplant they indeed were able to begin to recover T cells. Furthermore, despite marked lymphopenia including lack of circulating B cells, several patients were able to mount a SARS-CoV-2 antibody, suggesting antibody production from non-circulating lymph node or tissue-resident cells. The level and durability of this response remain uncertain. A similar experience has been reported in patients with multiple myeloma treated at Mount Sinai Health System also developed an antibody response (24). For patients who received lymphocyte-depleting chemotherapy or cellular therapies, elucidating lymphocyte requirements for adequate

401 immunologic control of the infection will be fundamental for developing clinical guidelines.
402 Given that some many transplant patients may have impaired humoral immunity due to prior
403 treatment history and/or cellular therapy, we predict that serologic conversation in the transplant
404 population will be lower than that of the general population.
405
406 Consistent with published data (10,11), detailed T cell analyses suggest an increase in CD8
407 TEMRA cells during SARS-CoV-2 infection, an indication of a terminally differentiated
408 phenotype (35). Early data suggest an exhausted phenotype in CD8 T cells in patients with
409 SARS-CoV-2 infection (10,11), which may reflect an active viral infection but may also be part
410 of the picture of why some patients with SARS-CoV-2 infection are unable to mount an adequate
411 antiviral response (8). We did not detect a clear association with degree of lymphopenia and
412 disease severity as has been shown previously (12), but this may be a reflection of our small
413 sample size combined with the immunologically complex nature of our population following
414 cellular therapies. We also acknowledge that the neutrophil to lymphocyte ratio may be
415 affected by a diversity of medical conditions, including active hematologic malignancy, and
416 may not be as informative in this population as compared with the general public.
417
418 Potential limitations of the interpretation of immunologic subsets in our patients include the
419 population heterogeneity, including a diversity of graft sources, distinct immunosuppression
420 regimens, combined with confounding clinical variables such as CMV reactivation, GVHD, and
421 disease relapse. As a result, we focused our analyses on trends pre-and post-COVID-19 within
422 the same patient and sought to contextualize our findings with available data from historical
423 controls, recognizing that a much larger cohort is needed to fully characterize risk factors for

disease severity. The decision to require swabbing within one week of immune profiling was an arbitrary cut-off, however because of the wide-range of COVID symptoms, a positive PCR, even if late into a patient's course, was an objective measurement of recent active infection; an area of active research is incorporating cycle threshold of the PCR to infer presence of viable virus (36).

Other limitations include lack of laboratory studies, including immunophenotyping, or diagnostic imaging in patients who had milder disease as these patients were able to continue to follow state and federal recommendations and were appropriately advised to remain isolated and to avoid non-urgent visits to the healthcare setting. The patients in this study were diagnosed during the initial surge in New York City and, as such, testing and treatment were based on the available data and safety guidelines of the time. Patients were identified for inclusion by positive PCR testing. As a result, additional symptomatic patients with COVID-19 may not have been included due to negative testing based on timing or sensitivity of the test. Asymptomatic patients may also have been missed as they were only tested prior to a needed procedure early during the pandemic when resources were more constrained. We acknowledge that diagnostic work-up and treatment in non-surge conditions and data obtained over time may change observed outcomes as further cases are diagnosed. As the median time from cell therapy to COVID-19 diagnosis was 782 days, the results may not be generalizable to the course of patients early after infusion. Furthermore, in the absence of systemic testing, we cannot assess a potential association between active malignancy and a higher likelihood of having COVID-19. Nevertheless, as we have included all of the patients who tested positive by PCR at our center, we are able to compare the outcomes of those who did and did not have active malignancy at the time of

their COVID-19 diagnosis. Finally, given the limited sample size and event rates, only univariable associations could be explored as multivariable modeling was infeasible.

The American Society for Transplant and Cellular Therapy (ASTCT), the European Society for Blood and Marrow Transplantation (EBMT), the Worldwide Network for Blood and Marrow Transplantation, and the Center for International Blood and Marrow Transplant Research (CIBMTR) continue to update guidelines for the treatment of COVID-19 in this population (37–40). Furthermore CIBMTR and EBMT continue to collect cases for multicenter analyses to improve outcomes for cellular therapy patients (41,42). An important issue will be for those with persistently positive NPS and the question of shedding of residual viral RNA versus infectious actively replicating virus (43–45). Some patients are not able to clear their NPS given their immune compromise, and the Ct value cutoff for safety and ability to resume treatment or discontinue precautions for cellular therapy patients are active areas of investigation at MSKCC.

In conclusion, patients who have received cellular therapies including allogeneic and autologous hematopoietic cell transplants and CD19 CAR T cell therapy were able to recover from COVID-19 infection and mount an antibody response, with similar overall survival to the general hospitalized population. Poor outcomes were more frequently seen in those with active relapsed disease and with risk factors akin to their non-cancer counterparts, such as comorbidities and neutropenia. Given the potential for prolonging survival and potential cure, it remains critical to safely continue treating patients with cellular therapies during the global pandemic and to determine successful interventions for those early after cellular therapy who remain immunocompromised.

Methods:

Patients who received Allo, Auto, or CAR T were identified from the MSKCC institutional database. Patients were included if they had a positive NPS for SARS-CoV-2 either at MSKCC or through the MSKCC Exchange system connecting our electronic record to outside electronic records at select institutions. Presumed positive patients were defined as having common COVID-19 symptoms with either a known exposure or imaging consistent with COVID-19.

The electronic medical record and institutional databases were abstracted for demographic information and medical history including comorbidities, treatment characteristics, and the presence and treatment of GVHD. For patients who underwent testing at outside locations, additional information and records were abstracted as available. Laboratory and radiology information at the time of SARS-CoV-2 testing and subsequent admission (if admitted), as well as COVID-19 specific treatments, complications, and outcomes were collected from March 11 through May 12, 2020. Follow-up SARS-CoV-2 testing was included through June 2, 2020. Severity of COVID-19 was defined as mild (no hospitalization required), moderate (hospitalization required), and severe (intensive care unit (ICU) required or goals of care changed to comfort care rather than escalation to the ICU). COVID-19 was considered resolved once clinical symptoms were no longer present.

Immunophenotyping of peripheral blood mononuclear cells via flow cytometry was performed in the MSKCC clinical laboratory. Lymphocyte panel: CD45 FITC (Becton Dickinson (BD), Franklin Lakes, NJ, #340664, clone 2D1), CD56+16 PE (BD #340705, clone B73.1; BD #340724, clone NCAM 16.2), CD4 PerCP-Cy5.5 (BD #341653, clone SK3), CD45RA PC7 (BD

#649457, clone L48), CD19 APC (BD #340722, clone SJ25C1), CD8 APC-H7 (BD #641409, clone SK1), CD3 BV 421 (BD #562426, clone UCHT1); naïve/effector T panel: CD45 FITC (BD #340664, clone 2D1), CCR7 PE (BD #560765, clone 150503), CD4 PerCP-Cy5.5 (BD #341653, clone SK3), CD38 APC (Biolegend, San Diego, CA, #303510, clone HIT2), HLA-DR V500 (BD #561224, clone G46-6), CD45RA PC7 (BD #649457, clone L48), CD8 APC-H7 (BD #641409, clone SK1), CD3 BV 421 (BD #562426, clone UCHT1). Lymphocyte populations were tracked over time and compared to historical control data for patients within two years post-transplant previously studied at MSKCC (14,46).

At MSKCC, NPS samples were collected using flocked swabs (Copan Diagnostics, Murrieta, CA) and placed in viral transport media (VTM). SARS-CoV-2 RNA was detected using the CDC protocol, targeting two regions of the nucleocapsid gene (N1 and N2), with the following modifications. Nucleic acids were extracted from NPS samples using the NUCLISENS EasyMag (bioMérieux, Durham, NC) following an off-board, pre-lysis step. Real-time reverse transcription polymerase chain reaction (PCR) was performed on the ABI 7500 Fast (Applied Biosystems, Foster City, CA) in a final reaction volume of 20-μL including of 5 μL of extracted nucleic acids. Samples were reported as positive if both the N1 and N2 targets were detected [Ct less than 40 with maximum of 45 cycles run]. Cts in patients with serial NPS were evaluated to explore the relationship between clinical outcomes and viral load. Serum or plasma was analyzed on the Abbott Architect i2000 analyzer (Abbott, Chicago, IL) in an automated two-step immunoassay for the qualitative detection of IgG antibodies to the nucleocapsid protein of SARS-CoV-2 using chemiluminescent microparticle immunoassay (CMIA) technology.

Descriptive statistics were used to summarize patient characteristics, lab values, and disease characteristics. Overall survival from the date of COVID-19 diagnosis to death or last contact date was estimated using Kaplan Meier methodology. Univariable associations between clinical characteristics and a composite endpoint of requiring a NRB or higher amount of oxygen and death was analyzed using Cox models, where time was defined from the date of COVID-19 diagnosis. Univariable associations between clinical characteristics and COVID-19 severity were assessed using the Kruskal-Wallis test, chi-square test of independence, and Fisher's exact test, as appropriate. Both sets of univariable analyses were performed among patients with labs performed within a week of COVID diagnosis. N-acetylcysteine treatment was given on a clinical trial (www.clinicaltrials.gov NCT04374461), while convalescent plasma (NCT04338360) and remdesivir (NCT04323761) were given through expanded access programs.

Study Approvals

This study was approved by the Institutional Review Board of MSKCC.

Author contributions:

GLS, SDW, GP, RT, CS, and MAP designed the study. GLS, SDW, YJL, RT, PD, JR, EB, TJ, CG, PM, MK, and LVR acquired the data. GLS, SDW JAL, SMD, PM, MK, and MAP analyzed the data. CC, JUP, IP, MS, SV, AD, TMH, MK, EP, and GP cared for the patients included in this study. GLS, SDW, and MAP wrote the manuscript, and YJL, RT, PD, JAL, JR, SMD, CC, JUP, IP, MS, EB, TJ, SV, AD, CS, JNB, SAG, CG, PM, TMH, MK, LVR, MVDB, EP, and GP critically reviewed the manuscript. GLS and SDW contributed equally to this work. GLS is listed first as she initiated the project.

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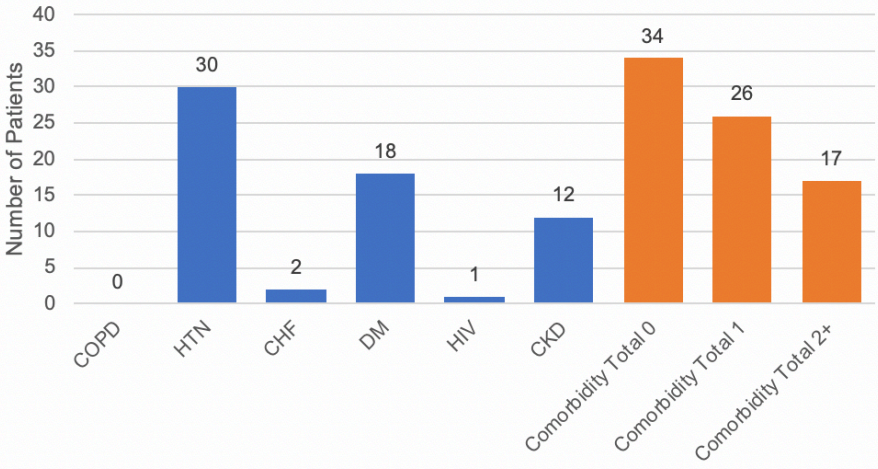
Figures:

Figure 1: Comorbidities at COVID-19 Diagnosis. 77 patients (Allo n=35, Auto n =37, CAR T n=5).



Abbreviations: COPD, chronic obstructive pulmonary disease; HTN, hypertension; CHF, congestive heart failure; DM, diabetes mellitus; HIV, human immunodeficiency virus; CKD, chronic kidney disease

Figure 2: Monitoring SAR-CoV-2+ patient over-time. Cycle threshold data over time for patients with two or more PCR swabs (n = 31). All negative values were given a value of 40 (Ct ≥ 40 = negative test at MSKCC, indicated with open symbol). Red * indicates subject deceased.

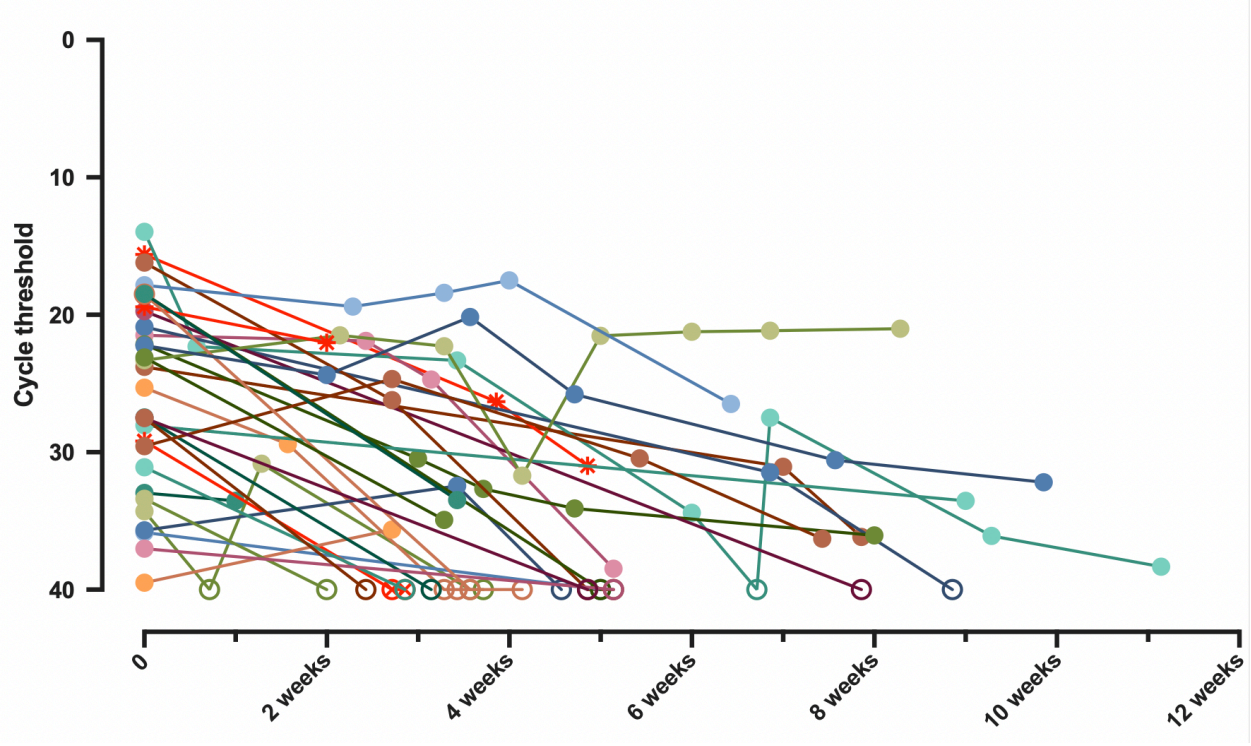
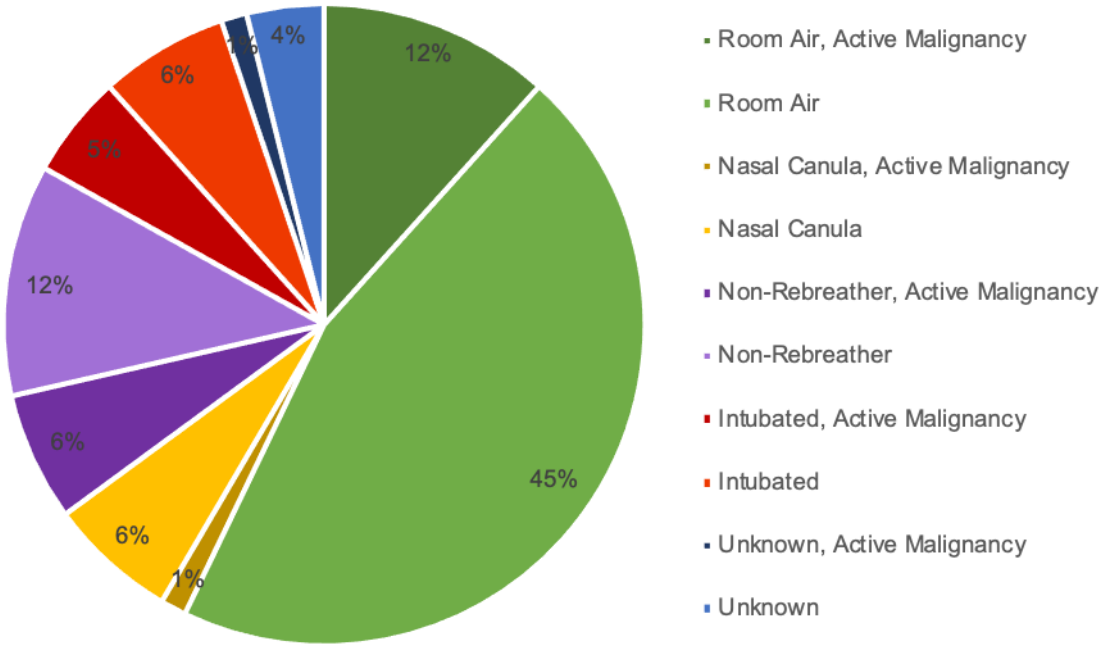


Figure 3: Outcomes and Disease Severity. A. Highest Supplemental Oxygen Given by Disease Status. B. COVID Disease Severity by Hematologic Malignancy Status. 77 patients (Allo n=35, Auto n =37, CAR T n=5). Severity of COVID-19 was defined as mild (no hospitalization required), moderate (hospitalization required), or severe (intensive care unit (ICU) required or goals of care changed to comfort care rather than escalation to the ICU).

A:



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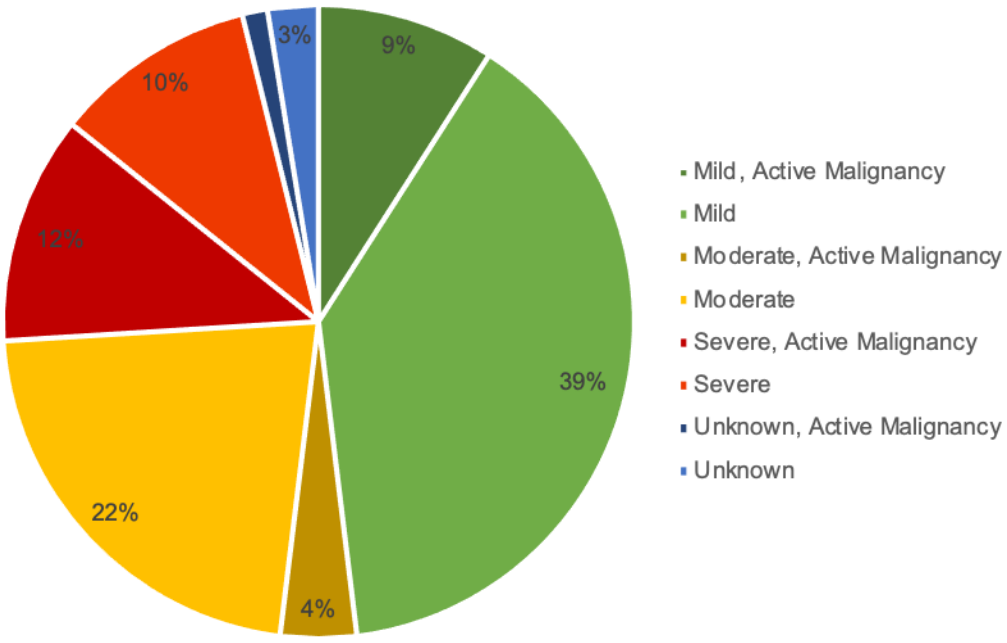


Figure 4: Status of COVID at Last Contact by Disease Status. 77 patients (Allo n=35, Auto n =37, CAR T n=5). COVID was defined as resolved at the end of clinical symptoms.

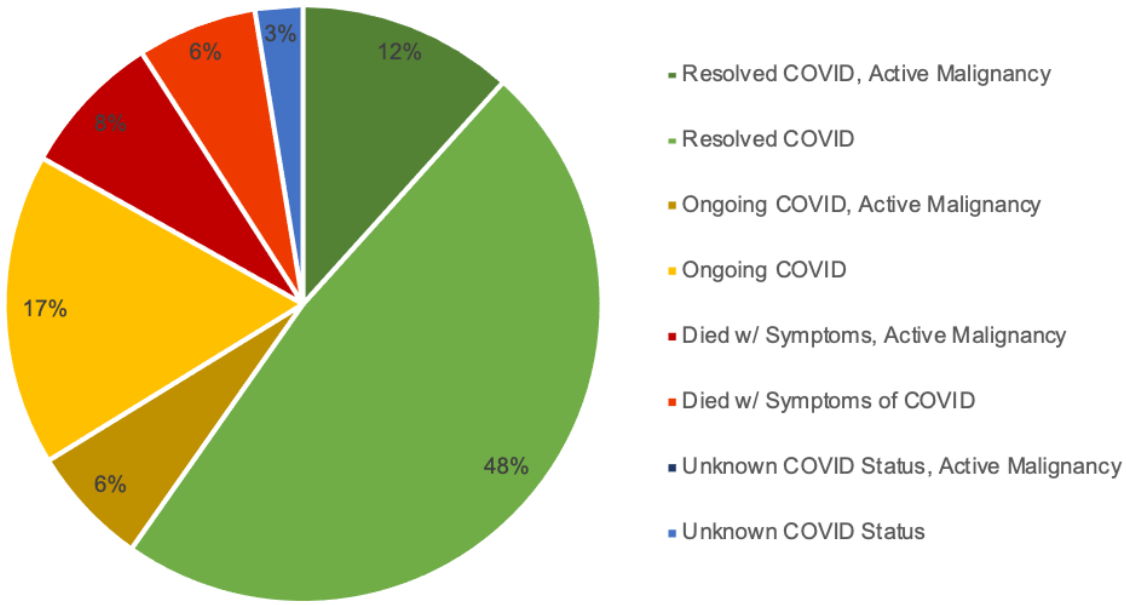


Figure 5: Overall Survival by Cell Therapy Type. 77 patients (Allo n=35, Auto n =37, CAR T n=5).

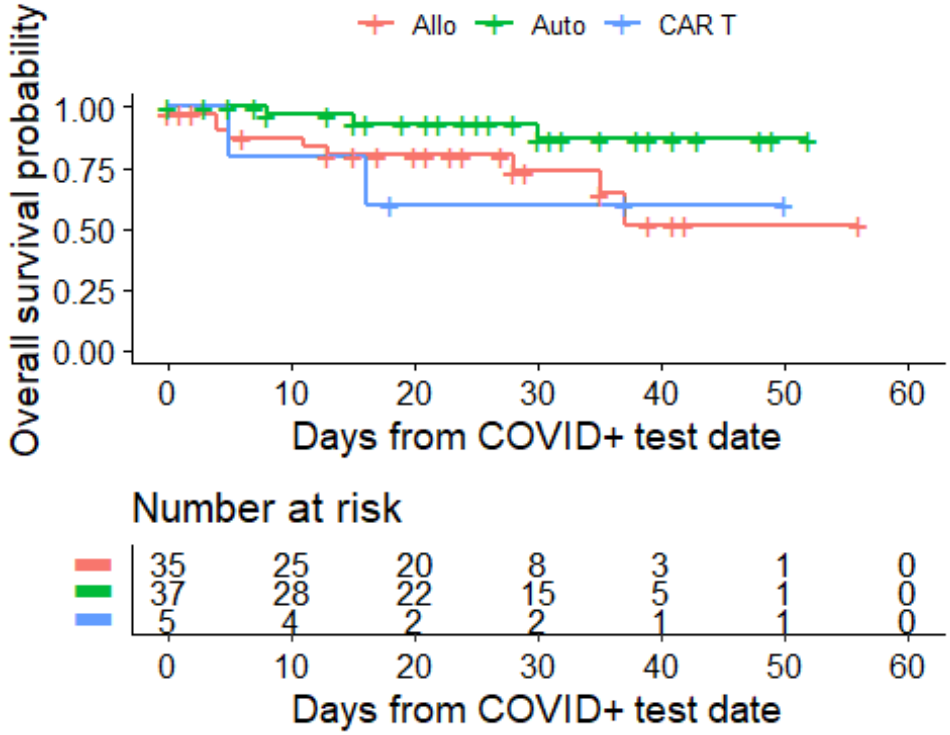
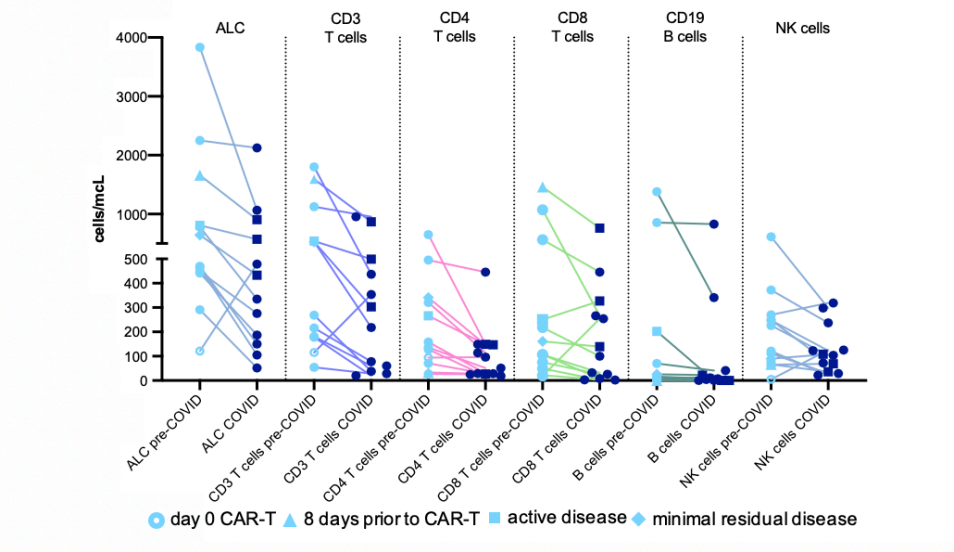


Figure 6: Immune subsets in SAR-CoV-2+ BMT patients. A. Absolute lymphocyte subsets in SAR-CoV-2+ patients compared to pre-COVID time point within one year of infection (n = 12). B. Absolute lymphocyte subsets within two years post-transplant in 8 SAR-CoV-2+ BMT patients (purple or blue symbols) compared to available data from historical controls (gray points, unmodified peripheral blood stem cell (PBSC) allogeneic transplant patients at MSKCC collected prior to the COVID pandemic); orange line indicates Loess curve of historical controls.

A.



B.

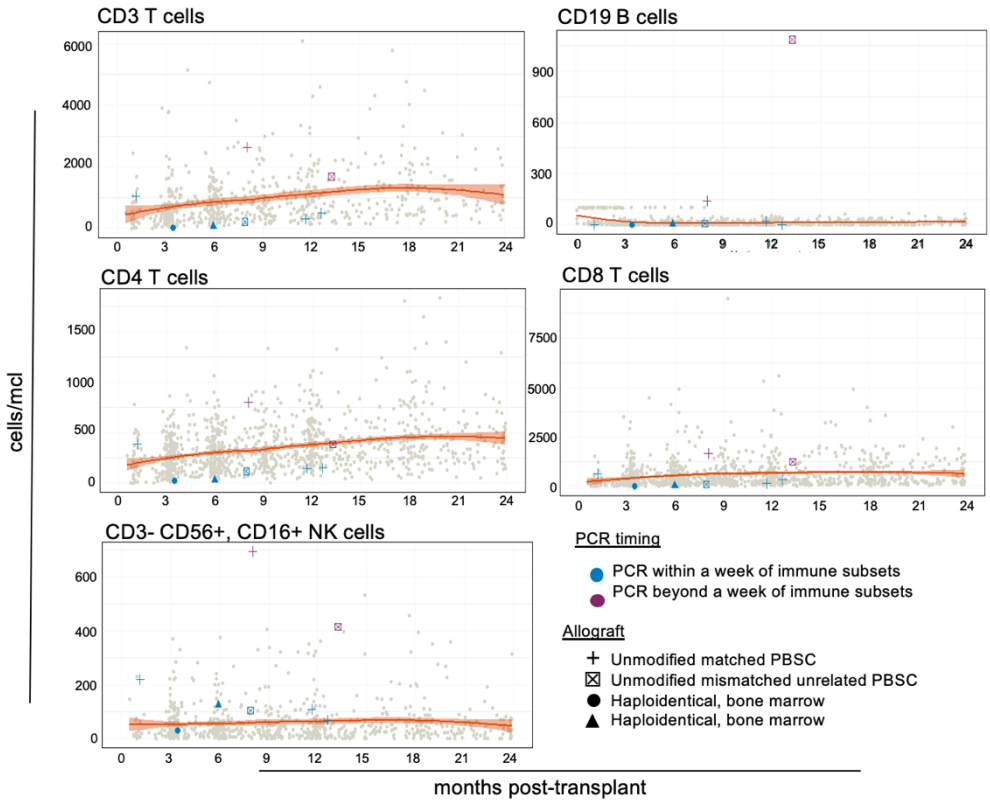
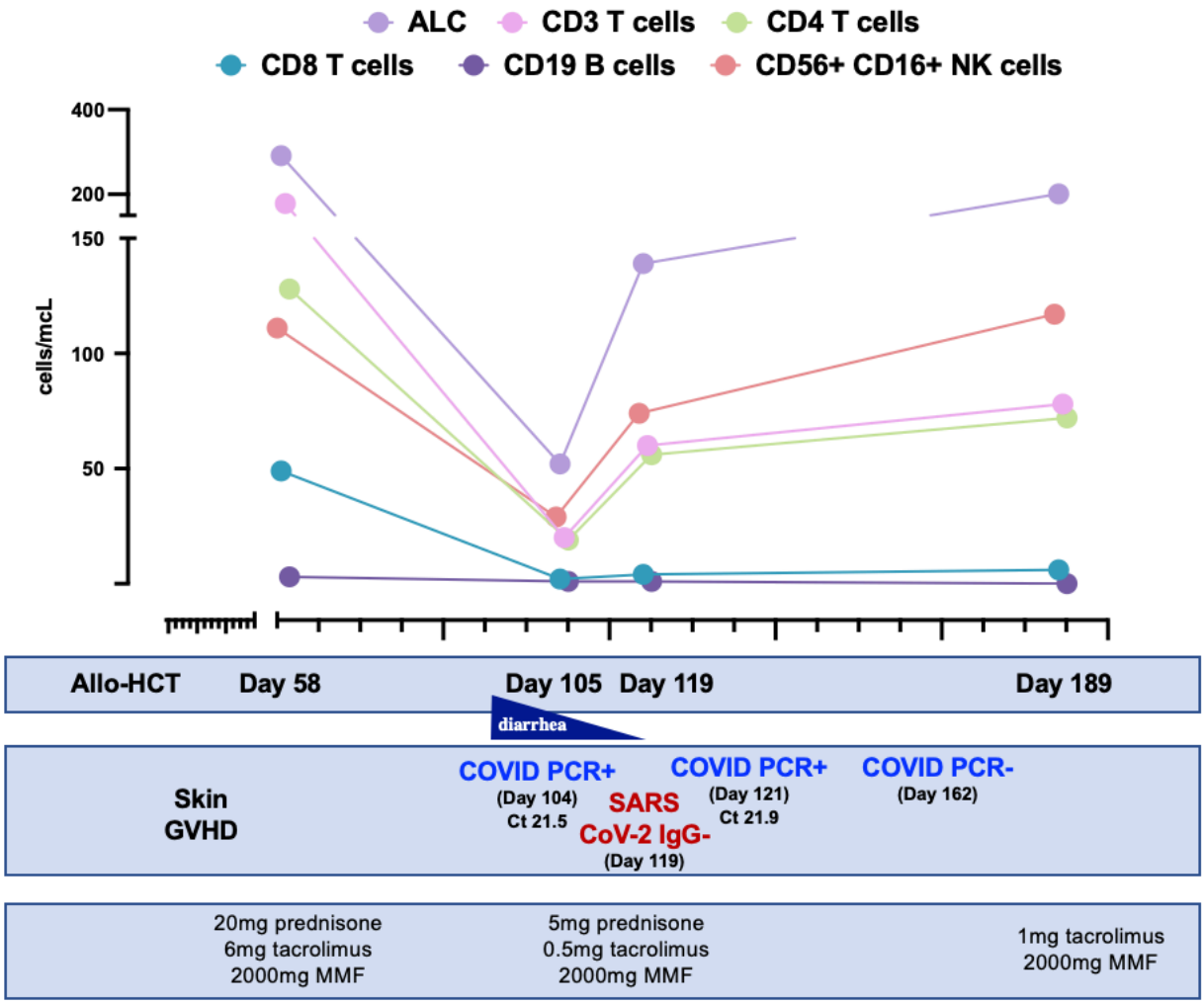


Figure 7: **Tracking lymphocyte subsets over time before, during, and in recovery from a COVID infection.** Allo patient who received a haploidentical transplant for AML. Available COVID PCR data with cycle threshold (Ct) and antibody status included.



Tables:

Table 1. Patient characteristics

Characteristic	Overall N = 77	Allo N = 35[1]	Auto N = 37[1]	CAR T N = 5[1,4]
Age at COVID-19 diagnosis	62 (52, 68)	60 (51, 65)	64 (52, 69)	63 (58, 74)
Male	49 (64%)	24 (69%)	22 (59%)	3 (60%)
Race[2]				
White	45 (58%)	25 (71%)	16 (43%)	4 (80%)
Black/African American	15 (19%)	4 (11%)	11 (30%)	0 (0%)
Asian/Far East/Indian Subcontinent	4 (5.2%)	2 (5.7%)	1 (2.7%)	1 (20%)
Ethnicity[2]				
Hispanic/Latino	15 (21%)	5 (15%)	10 (29%)	0 (0%)
Disease				
Multiple Myeloma	28 (36%)	2 (5.7%)	26 (70%)	0 (0%)
Non-Hodgkin's Lymphoma	20 (26%)	8 (23%)	7 (19%)	5 (100%)
Acute/Chronic Leukemia	19 (24%)	19 (54%)	0 (0%)	0 (0%)
Myelodysplastic Syndrome	4 (5.2%)	4 (11%)	0 (0%)	0 (0%)
Hodgkin Lymphoma	4 (5.2%)	1 (2.9%)	3 (8.1%)	0 (0%)
AL Amyloidosis	1 (1.3%)	0 (0%)	1 (2.7%)	0 (0%)
Myeloproliferative Disorder	1 (1.3%)	1 (2.9%)	0 (0%)	0 (0%)
Smoking status				
Current	1 (1.3%)	0 (0%)	1 (2.7%)	0 (0%)
Former	25 (32%)	13 (37%)	12 (32%)	0 (0%)
Never	51 (66%)	22 (63%)	24 (65%)	5 (100%)
Vaping status[2]				
Never	74 (96%)	35 (100%)	34 (92%)	5 (100%)
BMI[2]	27.4 (24.1, 30.6)	26.2 (23.6, 29.3)	28 (24.9, 30.8)	27.6 (20.5, 28.8)
Number of Comorbidities[3]				
0	34 (44%)	16 (46%)	17 (46%)	1 (20%)
1	26 (34%)	8 (23%)	14 (38%)	4 (80%)
2+	17 (22%)	11 (31%)	6 (16%)	0 (0%)
Time (days) post cell therapy				

Characteristic	Overall N = 77	Allo N = 35[1]	Auto N = 37[1]	CAR T N = 5[1,4]
<= day 100	5 (6.5%)	2 (5.7%)	1 (2.7%)	2 (40%)
101-180	5 (6.5%)	2 (5.7%)	2 (5.4%)	1 (20%)
181-365	10 (13%)	4 (11%)	6 (16%)	0 (0%)
366-1095	27 (35%)	14 (40%)	11 (30%)	2 (40%)
1096+	30 (39%)	13 (37%)	17 (46%)	0 (0%)
Donor Type				
Matched Related		9 (26%)		
Matched Unrelated		8 (23%)		
Mismatched Unrelated		7 (20%)		
Umbilical Cord Blood		7 (20%)		
Haploidentical		4 (11%)		
Conditioning				
Myeloablative		13 (37%)		
Reduced Intensity		17 (49%)		
Non-myeloablative		5 (14%)		
GVHD Prophylaxis				
CD34+ Selection		9 (25%)		
Post-Transplant Cyclophosphamide		7 (20%)		
Calcineurin inhibitor /Mycophenolate Mofetil based		9 (26%)		
Calcineurin inhibitor/Methotrexate based		10 (29%)		

[1]Statistics presented: n (%); median (IQR). [2]Unknown Race (n=2), Ethnicity (n=8), Vaping Status (n=1), Body mass index (BMI, N=6). [3]Comorbidities include hypertension, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, HIV (Human Immunodeficiency Virus), and chronic kidney disease. [4]One patient who had a CAR T had a prior Auto

Table 2: Univariable analysis of composite endpoint of requiring non-rebreather or more oxygen and death at lower level of oxygen.

Characteristic	N events	N	HR	95% CI	p-value
Hematologic Malignancy		74			0.6
Agressive NHL, Hodgkin Lymphoma, Indolent Lymphoma	9				
AML, ALL, MDS, MPN, Myelofibrosis, CML, CLL	10		1.16	0.47, 2.87	
Multiple Myeloma, POEMS, Primary AL Amyloidosis	6		0.70	0.25, 1.96	
Smoking status		74			0.4
Current or former	10				
Never	15		0.72	0.32, 1.60	
On Imid Therapy at COVID-19 Diagnosis	3	73	0.45	0.13, 1.49	0.15
Number of Comorbidities at COVID-19 Diagnosis		74			**0.004**
0	5				
1	10		3.36	1.15, 9.85	
2+	10		5.41	1.84, 15.9	
Infiltrates on Imaging at COVID-19 Diagnosis	14	39	3.08	1.00, 9.44	**0.032**
Time (days) post-cellular therapy		74			0.5
<= day 100	3				
101-180	1		0.29	0.03, 2.75	
181-365	5		1.08	0.26, 4.51	
366-1095	9		0.61	0.17, 2.28	
1096+	7		0.49	0.13, 1.90	
Race		67			0.3
Non-white	10				
White	13		0.62	0.27, 1.43	
Gender		74			>0.9
F	9				
M	16		1.04	0.46, 2.36	
BMI		70	0.95	0.87-1.04	0.2

Characteristic	N events	N	HR	95% CI	p-value
Hematologic malignancy active at time of COVID-19 diagnosis		74			0.11
N	15				
Y	10		1.96	0.88, 4.38	
Age at COVID-19 diagnosis		74	1.03	0.99, 1.06	0.11
ANC		50	1.15	1.02, 1.29	**0.043**
ALC		50	1.04	0.62, 1.74	0.9
Neutrophil to lymphocyte ratio at time of COVID-19 diagnosis		50	1.03	1.00, 1.07	0.081
Absolute CD4+		25	1.00	0.99, 1.00	0.3
Absolute CD8+		25	1.00	1.00, 1.00	0.7
Absolute CD19+		25	1.00	1.00, 1.00	>0.9
Absolute CD16+ CD56+ NK		25	1.00	1.00, 1.00	0.5
CD4:CD8 ratio		25	0.97	0.79, 1.18	0.7

Note: N events not shown for continuous variables. Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; NHL, non-Hodgkin Lymphoma; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; F, female; M, male; BMI, body mass index; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; Imid, immunomodulatory agent (ex. lenalidomide, pomalidomide)

Table 3. Immune profiling correlates within one week positive SARS-CoV-2 PCR

		Overall		Allo		Auto		CAR T
Characteristic	N	Median(IQR)	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
Absolute CD3+	25	354 (119,636)	12	365.5 (54.5, 526)	10	376.5 (212.8, 804)	3	354 (216,611.5)
Absolute CD4+	25	140 (51, 194)	12	146.5 (28.8, 202.8)	10	154 (119, 199.2)	3	51 (39, 73.5)
Absolute CD8+	25	221 (35, 327)	12	180 (26, 283.5)	10	212.5 (48.5, 614.5)	3	254 (140, 507)
Absolute CD19+	25	11 (0, 50)	12	9 (0.8, 26.8)	10	49.5 (5.2, 80)	3	0 (0, 0)
Absolute NK	25	100 (52, 151)	12	115.5 (92.2,252.2)	10	56 (38.5,116.5)	3	72 (54, 98.5)
CD4:CD8 ratio	25	0.9 (0.5, 1.6)	12	1 (0.6, 2.1)	10	0.7 (0.4, 1.4)	3	0.4 (0.2, 1.2)

Statistics presented: median (Interquartile range, IQR). Abbreviations: Allo, Allogeneic hematopoietic stem cell transplantation; Auto, Autologous hematopoietic stem cell transplantation; CAR T, CD19 directed chimeric antigen receptor T cell therapy; NK, Natural Killer