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Epidemiology of respiratory viral infections among hematopoietic cellular therapy and chimeric antigen receptor T-cell therapy recipients in the post COVID-19 era

Zainab Shahid[1,2], Judy Yan[3], Sigrun Einarsdottir[4], Shauna Usiak [3], Miguel-Angel Perales[2,4], Jae Park[5], Saad Z. Usmani[6], Eytan Stein[7], Gilles Salles[8], Ann Jakubowski[4], Esperanza Papadopoulos[4], Ivan Millard[8], Sergio Giralt[4], Gunjan L. Shah[4], Mini Kamboj[1,2]

[1] Infectious Disease Service, Memorial Sloan Kettering Cancer Center, New York, NY
[2] Department of Medicine, Weill Cornell Medical College, New York, NY, 10065, USA
[3] Infection Prevention and Control, Memorial Sloan Kettering Cancer Center, New York, NY
[4] Adult Bone Marrow Transplantation Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, 10065, USA,
[5] Cellular Therapy Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, 10065, USA,
[6] Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, 10065, USA,
[7] Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, 10065, USA,
[8] Division of Hematological Malignancies, Memorial Sloan Kettering Cancer Center, New York, NY, 10065, USA

Authors Contribution:
Z.S and M.K conceived and planned the study. Z.S and J.Y collected data. Z.S, J.Y and M.K planned the analysis. J.Y performed the analysis. S.E, S.U, M.P, J.P, S.U, E.S, G.S, A.J, E.P, S.P, S.G, G.S reviewed the manuscript and provided feedback.

Corresponding Author: Zainab Shahid, MD, email: shahidz@mskcc.org
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Key points:

- The epidemiology of infection after the COVID-19 pandemic has changed, SARS-CoV-2 infection remains the most common RVI observed post-TCT

- Non-COVID RVIs (including RSV, infleunza, parainfluenza, human metapneumovirus and adenovirus) were associated with the highest risk of severe infection.

- An absolute lymphocytes count of less than 200 cells/μL was a significant risk factor for severe RVIs in the overall study population.

Abstract:

Respiratory viral infections (RVIs) remain a source of morbidity among hematopoietic cell transplant (HCT) or chimeric antigen receptor (CAR) T-cell therapy recipients. This study aims to understand the post-pandemic RVI epidemiology in cellular therapy recipients. IRB-approved retrospective study of consecutive HCT and CAR T-cell therapy recipients diagnosed with RVI within 100 days of cellular therapy in a single academic center from January 1, 2022, to August 2, 2024.

Among 2072 HCTs and 545 CAR T-cell treatments, 194 RVIs were identified within the first 100 days (cumulative incidence of 7.4%). The incidence of RVI was 12.7% in CAR T (n=70), 7.8% in allogeneic HCT (n=69), and 4.7% in autologous HCT (n=55) recipients. SARS-CoV-2 was the most common pathogen (43%), followed by parainfluenza virus (21%) and RSV (16%). Most RVIs (79%) were community-acquired with a median onset of 54 days post-infusion. Among the194 episodes, 151 (78%) were upper respiratory tract infections, and 43 (22%) were lower respiratory tract infections (LRTIs); 49% (21/43) of LRTIs were severe. In multivariate analysis, severe RVI was associated with the use of tocilizumab within 30 days of RVI (OR 4.84 95% CI 1.12-20.96, p=0.035), low ALC (<200 cells/microL; OR 6.82 (95%CI 1.89-24.67, p=0.003), and infection with non-SARS-CoV-2 viruses (OR 10.26, 95% CI 2.37-44.43, p=0.002).

Early RVIs occurred most frequently in CAR T recipients, and SARS-CoV-2 was the most common pathogen. Approximately one quarter of medically attended RVI involves the lower respiratory tract. Severe disease is associated with infections with non-SARS-CoV-2 viruses and profound lymphopenia.

Introduction.

In the last decade, novel discoveries and new knowledge have advanced clinical approaches in cellular therapies. Expanding age and disease indications, new transplant modalities, and progress in approaches to graft vs. host disease (GVHD) prevention and management have led to an overall trend towards improved patient outcomes [1,2]. Despite these advances, infections remain the leading cause of non-relapse mortality after allogeneic and autologous HCT [3,4]. In particular, the burden, risks, and management of respiratory viral infections (RVIs) in hematopoietic cellular therapy (HCT) remains challenging[5]. RVIs are associated with poor pulmonary outcomes including airflow obstruction, bronchiolitis obliterans syndrome and mortality post HCT[6]. In the post COVID-19 pandemic era (2023-2024 season) an international cohort study of 1312 hematological malignancy patients including HCT and CAR T recipients, reported an overall mortality rate of 10.6% with community acquired respiratory viruses, with highest mortality rate with parainfluenza virus (21.3%), highlighting variable impact of respiratory viruses[7]. Understanding the impact of novel transplant strategies such as post-transplant cyclophosphamide dominant graft vs. host disease (GvHD) prophylaxis[8], alternative donors[9], expanding menu of GvHD treatments[10], on RVI outcomes remains an unmet need.

Among the newer treatments, seven CAR T- cell therapies targeting CD19 and BCMA have been approved for the management of refractory or relapsed plasma cell and lymphoid malignancies since 2017 [11]. Despite the successes of this treatment modality, especially for those with limited therapeutic options, toxicities and infection risks pose a significant challenge. Post-approval studies show that infections are the main cause of

non-relapse mortality in the first year after CAR T [12]. Furthermore, infection within the first 100 days is an independent predictor of overall survival beyond 100 days after CAR T. Several factors influence this risk, including the baseline host profile such as advanced age, disease status, and prior treatments; the intensity of lymphodepletion; immune effector cell-associated toxicities, including IEC-HS, CRS, and ICANS; steroid use; and hypogammaglobulinemia [13,14]. Similarly, studies among multiple myeloma patients show that 48% of patients treated with B-cell maturation antigen (BCMA) CAR T develop viral infections of the respiratory tract[15]. Collectively across these studies, viral infections, due to community respiratory viruses, account for more than half of all infections and are especially common between 30-100 days post-treatment[16].

Beyond the global description of infectious risks, there is limited published experience on the specific epidemiology of seasonal respiratory viruses after CAR T, and much of the prevention and management is extrapolated from approaches applied in allogeneic and autologous hematopoietic stem cell transplant recipients, where the major studies of RVI impact were conducted in the pre-pandemic period. While many of the risks are expected to overlap across the CAR and transplant populations, a deeper understanding of RVI frequencies, clinical presentation, risks, and their differences or similarities from HCT is important to inform optimal prevention and management approaches tailored to the unique needs of present-day cellular therapies.

To summarize, the evolving landscape of cellular therapies and host factors, as well as the post-pandemic changes in RVI epidemiology, highlights the critical need to understand RVI incidence and outcomes among these vulnerable patients to inform the most effective prevention and management strategies. In the present study, we

describe the post-pandemic risks and predictors of severe RVIs in the first 100 days after hematopoietic stem cell transplant and chimeric antigen receptor therapies received between 2022-2024.

Methods:

Patients and Study Design:

This is a single-center retrospective analysis of consecutive HCT and CAR T-cell therapy recipients from January 1, 2022, to August 2, 2024, who were diagnosed with an RVI (lab confirmed by viral PCR detection) within the first 100 days of their cellular therapy. Non-SARS human coronaviruses (HCV) and human rhinovirus (HRV) were excluded, as high asymptomatic carriage and prolonged shedding preclude reliable attribution of clinical infections to detection. SARS-CoV-2 (COVID-19), Influenza A and B, Respiratory Syncytial Virus (RSV), Parainfluenza virus (PIV) 1,2,3, and 4, and human metapneumovirus (hMPV) and adenovirus (ADV) infections were analyzed for the study. Data were collected by retrospective chart review after IRB approval.

Definitions:

Upper respiratory tract infection (URTI) was defined as viral PCR detection from a nasopharyngeal sample from a symptomatic patient, without any radiographic abnormalities or viral detection from the lower airway. If new radiographic changes were noted in a patient with URTI, or a virus was isolated from a lower respiratory tract sample (bronchoalveolar lavage [BAL], lung biopsy, or autopsy specimen), with or without radiographic abnormality, the illness was defined as lower respiratory tract infection (LRTI), respectively[17]. Both chest X-rays and chest computed tomography

results were included if completed within 2 weeks of the viral detection. The day of LRTI diagnosis was defined as the date when a respiratory virus was detected in the lower tract specimen or the date the radiographic abnormality was detected.

RVI was categorized as hospital-acquired when symptoms developed three or more days after hospital admission, or if a readmission with newly diagnosed RVI occurred within three days of discharge. Severe RVIs were defined as both upper and lower RVIs that required hospitalization and supplemental oxygen, or ICU admission. Infections occurring on days 0-30 after HCT or CAR T infusion were classified as early, and those on days 31-100 as late. Severe and non-severe RVIs included both URTI and LRTI in the outpatient setting.

Statistical Analysis:

Descriptive statistics were used for patient demographic data. Lowest value of the absolute neutrophil counts (ANC) and absolute lymphocyte count (ALC) +/- 7 days of RVI was captured for analysis. Hospitalization and ICU admission was captured for 2 weeks after RVI diagnosis. Univariable analysis was initially performed to assess potential risk factors for severe RVI. Variables found to be significant at $p<.05$ were then entered into a multivariable logistic regression model using a forward likelihood ratio algorithm. Due to the relatively small sample size in each categorical risk factor, Firth's penalized likelihood was employed in all analysis to account for parameter estimation bias. Results from the regressions models are reported as odds ratios (ORs) with 95% confidence intervals (CIs) and 2-sided P values for statistical significance. To evaluate

multicollinearity, we examined the variance inflation factor (VIF). The validity of the regression model was evaluated using the Hosmer-Lemeshow test. All data analyses were performed using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

Results:

During the study periods, 2,072 transplants (889 allogeneic HCTs and 1183 autologous HCTs) and 545 CAR T procedures were performed at our institution. Analyzing only the pathogens of interest, a total of 194 RVIs were observed within the first 100 days in 194 unique patients with a cumulative incidence of 7.4% during the observation period. Patient characteristics are listed in Table1(additional details **Supplemental Table 1**). The median time to any RVI from cellular therapy was 45 days (range 0-99); 37% (72/194) occurred in the first 30 days. SARS-CoV-2 accounted for the largest proportion of RVIs (84 episodes; 43.2%), followed by PIV (41 episodes; 21.1%), RSV (32 episodes; 16.4%), adenovirus (15 episodes; 7.7%), hMPV (12 episodes; 6.1%), and influenza A and B (10 episodes; 5.1%). Figure 1 illustrates the distribution of different RVIs over the study period.

RVI severity by viral etiology and infection onset

Among the 194 episodes, 151 (78%) were URTIs, and 43 (22%) were LRTIs. Among LRTIs, 49% (21/43) were severe, with 14 requiring supplemental oxygenation (high flow, n=4) or mechanical ventilation (n=3). The median onset of severe RVI from cellular therapy was 16 days (range 1-82). PIV was the most common cause of severe infection (n=9,43%), followed by adenovirus (n=6, 29%) and RSV (n=4, 19%).

By onset, 79% (153/194) of the RVI's were community acquired compared to 21% (41/194) hospital acquired infections. Distribution of nosocomial and community-acquired viruses is listed in **Table 2**. Seventy-one percent of the nosocomial infections (15/21) were severe compared to 29% (6/21) of community-acquired infections.

More than one-third (72, 37%) of the infections were observed in the first 30 days of cellular therapy infusion. Earlier infections were more severe compared to late infections (day 31-100) (14/72, 19% vs. 2/122, 6%). The distribution of community acquired, and nosocomial infections was equal among early infections (36 each). Early infections were more common among autologous HCT recipients (29/72, 40%), followed by CAR T recipients (27/72, 38%), and then allo HCT recipients (16/72, 22%). The distribution of pathogens observed in the early risk period was COVID-19 (37), followed by PIV (11), RSV (8), Adeno (6), and 3 RVI episodes for influenza and hMPV each.

Observations by pathogen

Of the 84 COVID-19 infections, 63 (75%) were treated (51 received antivirals, and 12 received monoclonal antibody). None of the COVID-19 infections were severe. RSV infections (n=32) were treated with antiviral, with or without immunoglobulins, in half the cases (n=17). Except for one patient, all others diagnosed with influenza received antiviral treatment (n=9). Six of the 15 patients (40%) with adenovirus infection had concurrent viremia. Adenoviral RVIs had the highest proportion of severe infection (40%), followed by PIV (21%). Treatment details by pathogen types are described in Table 3, and Table 4 describes the disease severity by pathogen type.

RVI characteristics by underlying treatment

Among allogeneic and autologous HCT recipients, we identified 69 and 55 infections with a cumulative incidence of 7.8% and 4.7%, respectively. For the CAR T cohort, 70 infections were identified with a cumulative incidence of 12.7%. The median time to infection was shortest in the autologous HCT group at 30 days, followed by the CAR T group and the allogeneic HCT group, at 42 and 54 days, respectively. The distribution of community-acquired vs. hospital-acquired infections was similar in the overall cohort, with most infections originating in the community (76%-88%) (Table 5).

Risk Factor Analysis

We next identified risk factors for severe RVI compared to non-severe RVI for all patients (**Supplemental Table 2**). In the univariate analysis use of tocilizumab (OR 5.29, 95%CI 1.95-14.36, p= 0.001), ANC <500 cell/mL (OR 5.08, 95% CI 1.94-13.3, p=<0.001) , ALC <200 cells/mL (OR= 9.43, 95%CI 3.17-28.11, p= <0.001), infection with non-COVID respiratory pathogen OR 7.03 95%CI 1.81 - 27.34, p=0.005 and steroid use within 14 days before RVI (OR 4.32, 95%CI 1.7-11.2, p=0.002) was associated with severe infection. In the multivariate analysis covariable adjustment, factors that predicted RVI severity were use of tocilizumab in the last 30 days before RVI (OR 4.84 95% CI 1.12-20.96, p=0.035), low ALC (<200 cells/microL) with of OR 6.82 (95%CI 1.89-24.67, p=0.003) and infection with non-COVID viruses (OR 10.26, 95% CI 2.37-44.43, p=0.002).

Exploratory subgroup analysis was performed for each cohort. In the allogeneic HCT group, the univariate analysis of post-transplant RVI episodes, most demographic, disease-related, and transplant-specific variables, including age, sex, race, underlying malignancy, HCT-CI, KPS, conditioning intensity, HLA matching, and comorbidities,

were not significantly associated with severe disease (all p >=0.05). Tocilizumab within 30 days prior to RVI was significantly associated with increased odds of severe RVI (OR 15.5, 95% CI: 1.31–184.31, p = 0.030). Other factors associated with increased disease severity included ALC<200 cells/μL (OR 18.0, 95% CI: 2.74 - 117.62, p = 0.003), ANC < 500 cells/μL (OR 10.64, 95%CI: 1.17 - 66.1, p=0.011) and RVI with adenovirus (OR 16.7, 95%CI 2.82-98.9, p=0.002) (**Supplemental Table 3**). In the autologous HCT group, rituximab within 6 months prior to infection showed a borderline significant association with increased severity (OR 7.38, 95% CI: 1.00–54.4, p = 0.050). PIV infection was associated with increased odds of severe disease (OR 7.00, 95%CI: 1.12 - 43.7, p = 0.037). No significant associations were observed with renal dysfunction, IgG level, ALC, ANC, or other viral etiologies (**Supplemental Table 4**) in this subgroup. In the CAR T cohort, univariate analysis did not identify significant associations between RVI severity and demographic characteristics, comorbidities, timing of infection, or performance status (all p > 0.05). Tocilizumab administration within 30 days prior to RVI was significantly associated with increased odds of severe disease (OR 6.76; 95% CI: 1.39–32.9; p = 0.018), whereas ALC < 200 cells/μL was associated with a higher risk for severe RVI (OR 11.76, 95%CI: 1.83 - 75.5, p = 0.009). No associations were observed with CRS grade, ICANS, or specific viral pathogens. A borderline association was noted for adenovirus infection (OR 6.54; p = 0.060) and CD19-targeted CAR T therapy (OR 0.16; p = 0.068), though these did not reach statistical significance **(Supplemental Table 5**).

Clinical Outcomes

RVI was associated with causal mortality in two patients in the entire cohort. One death was attributed to early RSV infection acquired on day 12 post-transplant (autologous) in a multiple myeloma patient. The second death occurred in a patient with AML with fulminant adenovirus infection 23 days after an allogenic HCT (mismatched unrelated, flu/cy TBI with post-transplant cyclophosphamide). RVI timing (early vs. late) did not impact the survival probability (Figure 2). Infection with non-SARS-CoV-2 viruses was associated with an overall higher 1-year mortality compared to patients with COVID-19, but it was not statically significant (p=0.1112) (Figure 3). The relative risk (RR) of mortality associated with severe RVI within 30 days was 4.13 (95% CI 0.80-21.17, p=0.090); while the RR of mortality within 100 days was 1.77 (95% CI 0.55-5.64, p=0.338).

Discussion

In the present single-institution study of over 2500 cellular therapy recipients, including > 500 CAR T treated individuals, the cumulative risk of early RVI due to a major pathogen within the first 100 days was 7.4 %, with 37% of the infections occurring within 30 days of cellular therapy infusion. SARS-CoV-2 and parainfluenza were the most frequently detected viruses, and most infections originated in the community. Overall, 22% of medically attended infections had evidence of LRTI, and 11% of the patients developed severe RVI. The odds of severe infection were almost twice as high in the first 30 days after cellular therapy. Severe lower airway disease was most frequently observed in non–SARS-CoV-2 and hospital-acquired RVIs, especially among patients with profound lymphopenia. In terms of modality, cumulative RVI incidence and severity tended to be higher in allogenic and CAR T recipients than in autologous HSCT. Our

combined risk factors analysis points out that in addition to the pathogen, the host immune system plays a key role in RVI severity. Finally, the all-cause mortality at 1 year after cellular therapy was not observed to be higher in patients with RVI within 100 days compared to those without RVI in this period, although those with non-SARS-CoV-2 infections had higher all-cause mortality at a year compared to those with COVID-19.

In the last two decades, advances in viral diagnostics and the emergence of new pathogens (e.g., metapneumovirus and SARS-CoV-2) have broadened our understanding of respiratory viral illnesses after cellular therapies[18,19]. Advances in molecular diagnostics, together with evolving prevention and treatment strategies, have enabled earlier detection and improved management of RVIs. As newer cellular therapies and transplant techniques have continued to evolve, the use of reduced intensity myeloablative regimens has become more common, transplants are being performed in the outpatient setting, increasing the exposure to community acquired infections. Furthermore, a more protracted immune reconstitution with post-transplant cyclophosphamide and expanding CAR T use has introduced important shifts in the epidemiology and outcomes of RVI's. Several recent studies, including our current data, demonstrate that the progression to lower airway infection and severe disease continues to be exceptionally high in the initial period after cellular therapy, primarily driven by severe lymphopenia and infection with non-SARS-CoV-2 pathogens, especially parainfluenza viruses, for which there are currently no effective treatment options available.

According to a large national claims database, 10% of 13,363 allogeneic HCT recipients in 2011-2018 had an RVI diagnosis in the first year after transplant [5,20]. Up to 50% of

patients with early RVIs have evidence of lower airway involvement[21]. Similar to our findings, other studies have shown a higher RVI incidence in allogeneic HCT recipients when compared to autologous HCT recipients[22]. Some of the key risk factors for LRTI progression in prior studies include early infection, allogeneic transplant recipients, and acute or chronic GVHD. Not all these variables were significant or could be rigorously assessed in our study due to a primary focus on early infections due to major pathogens only, and a strict criterion for severe RVI, even though there was a numerically higher likelihood of severe RVI with all these factors [19,22-25].

The current study is among the large-scale analyses of RVI impact in 545 recipients of CAR T therapies. We found that the cumulative incidence of RVI at 100 days from major pathogens was twice as high in CAR T recipients compared to HCT recipients (12.7% vs. 6%, respectively). It is important to note that RVIs are the most prevalent infections among BCMA and CD-19 CAR T cell therapy recipients[26,27]. In a previous report of 200 CAR T recipients, 23% experienced at least one RVI, and most infections, like in our study, occurred late (>30 days) (median,130 days)[28]. Other reports have estimated that viral infections comprise about half of all post-CAR infections, and ~80% of those are RVIs, with a comparable distribution between early and late RVIs [28-31] . Multiple risk factors seem to predict severe disease in CAR recipients, including hypogammaglobulinemia, prior transplant, cytokine release syndrome and ICANS, corticosteroid use, and hemophagocytic lymphohistiocytosis and lymphopenia[26,28,32]. It is important to note that early RVIs post CAR T itself are a risk factor for late respiratory tract infections beyond day 100 [26]; however, the long-term impact of RVIs among CAR T cell therapy recipients remains unknown. Much like HCT recipients, a major concern

with RVIs among CAR T cell therapy recipients is its progression from URTI to LRTI and the consequences of secondary infections and cardio-pulmonary dysfunction[16]. Our study found that the use of tocilizumab within 30 days of RVI diagnosis and lymphopenia are associated with severe disease. Due to the limited number of severe infections and the heterogenous representation in our CAR T sub cohort, we cannot robustly evaluate the risk factors for severe disease and long-term complications. However, we demonstrate the substantial impact of RVIs, which seem to occur more frequently than in HCT recipients, and match the outcomes observed among allogeneic HCTs.

Several limitations warrant acknowledgements. Our analysis is limited by the small number of severe episodes (n=21), which yields wide confidence intervals and precludes multivariable adjustment. Unadjusted estimates are therefore suspectable to confounding. These findings from a single center are hypothesis generating and confirmation in a larger multicenter cohort is required. We reported small number of infections with important pathogen like influenza and RSV; this could be related to the study period and study findings should be interpreted with knowledge of local epidemiology. There is a risk of misclassification of RVI severity given the possibility undiagnosed concomitant infections. We did not have access to immunization records for all patients and are unable to assess any potential beneficial impact. Despite the size of the cohort, early infections (within 100 days), which constitute the highest risk period, represented only 37% of all infections. The study was performed at a single academic center with focus on cancer population, this limits the generalizability of our

findings to broader and more heterogeneous patient population, including those managed in community or non-oncology settings.

In conclusion, RVIs with in first 100 days from major viruses cause substantial morbidity in cellular therapy recipients with a higher cumulative frequency of infection in CAR T recipients and especially worse outcomes with non-SARS-CoV-2 infections, such as parainfluenza, RSV, and adenovirus. Lymphopenia is a consistent risk factor for severe disease. Our findings provide a framework for identifying patients at high risk of severe RVIs in the current era, supporting prioritization of infection preventative strategies including active and passive immunization for these patients in future studies. Better prevention and therapeutic strategies for parainfluenza, RSV, and adenovirus infections are essential to improve patient outcomes.

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Table 1: Baseline Characteristics of Study Participants

All Transplants: N=194	
Characteristic	**N (%)**
Age at BMT, years, median (IQR)	61.0 (17.1)
Gender	
Male	110 (56.7)
Female	84 (43.3)
Race	
Asian	21 (10.8)
Black	31 (16.0)
White	123 (63.4)
Other	11 (5.7)
Unknown	8 (4.1)
Underlying Malignancy	
Multiple myeloma	68 (35.1)
Leukemia MDS	58 (30.0)
Lymphoma	46 (23.7)
B-ALL	2 (1.0)
Other	20 (10.3)
Type of Cellular Treatment	
Allogeneic HCT	69 (35.6)
Autologous HCT	55 (28.3)
CAR-T	70 (36.1)
Smoking History	
Current	20 (10.5)
Former	49 (25.7)
Never	122 (63.9)
Comorbidities	
Diabetes	34 (17.5)
COPD	8 (4.1)
CKD	94 (48.5)
HTN	132 (68.0)
CHF	26 (13.4)
KPS Scores	
<90	81 (59.1)
>=90	56 (40.9)
Laboratory Values at The Time Of RVI (+/-7days)	
ANC<500 cells/mcL	31 (16.1)
ANC>=500 cells/mcL	162 (83.9)
Missing/not performed	1
ALC<200 cells/mcL	67 (34.7)
ALC>=200 cells/mcL	126 (65.3)
Missing/not performed	1
CD4<200 cells/mcL	26 (61.9)

CD4>=200 cells/mcL	16 (38.1)
Missing/not performed	152
IgG<400 mg/dL	48 (35.3)
IgG>=400 mg/dL	88 (64.7)
Missing/not performed	58
Creatinine<1.1 mg/dL	141 (72.7)
Creatinine>=1.1 mg/dL	53 (27.3)
Antiviral Treatment	
Y	72 (37.1)
N	122 (62.9)
Infection Period	
0-30 days	72 (37.1)
31-100 days	122 (62.9)
Median time to RVI infection (days, range),	45 (0-99)
Steroid use within 14 days prior to RVI	
Y	67 (34.5)
N	127 (65.5)

Table 2: Distribution of Respiratory Pathogens by origin of infections in descending order

Community Acquired Infections N=153 (pathogen, n, %)	Nosocomial Acquired Infections N=41 (pathogen, n, %)
COVID 67 (44%)	COVID 17 (41%)
PIV 33 (22%)	Adenovirus 10 (24%)
RSV 28 (18%)	PIV 8 (20%)
Influenza 10 (6.5%)	RSV 4 (10%)
HMPV 10 (6.5%)	HMPV 2 (5%)
Adenovirus 5 (3%)	Influenza 0 (0%)

COVID-19 SARS-CoV-2 Infection, PIV parainfluenza virus, RSV respiratory syncytial virus, hMPV human metapneumovirus,

Table 3: Utilization of antiviral and immunoglobulin therapy for treatment of RVIs

RVI pathogen	Antiviral utilized
COVID-19 N=84	Antiviral N=63 Paxlovid=21 Molnupravir= 11 Remdisivir= 18 Monoclonal antibody Bebtelovomib=9 Sotrovimab=3
PIV=41	IVIG=1
RSV N=32	Oral Ribavirin alone =8 IVIG alone =1 Oral Ribavirin +IVIG=8
Adeno=15	Cidofovir=1 (eventual disseminated adenovirus infection)
HMPV=12	None
Influenza=10	Oseltamivir =9

Table 4: Details of pathogen by severity

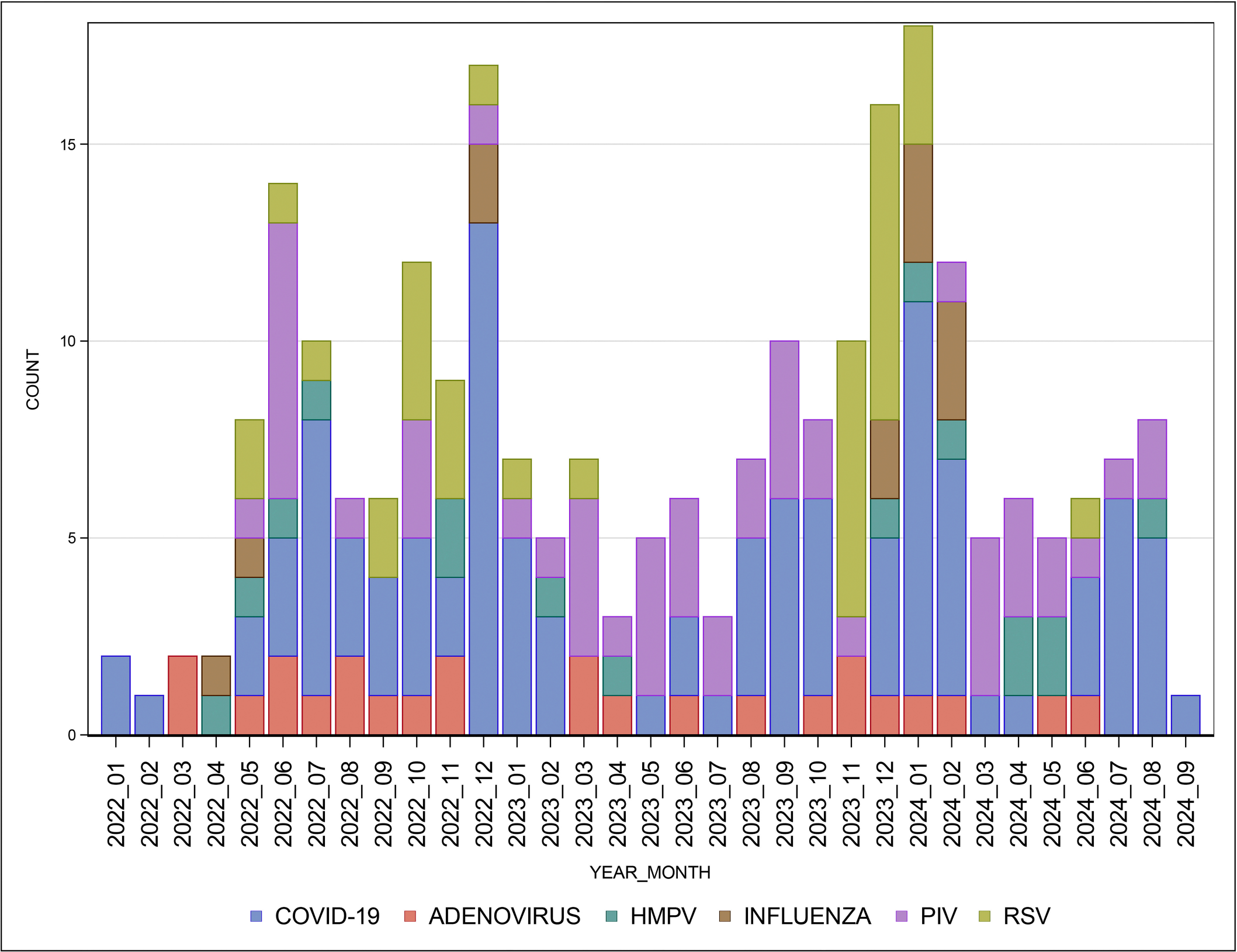
Distribution of Pathogen	Total number	Severe	Non-Severe
COVID19	84	2 (3%)	82 (97%)
PIV	41	9 (22%)	32 (78%)
RSV	32	4 (12%)	28 (88%)
Adenovirus	15	6 (40%)	9 (60%)
HMPV	12	0(0%)	12 (100%)
Influenza	10	0 (0%)	10 (100%)

Table 5: Clinical Observations Notable for Each Treatment Modality

Clinical Variable	Auto N, %	Allo N, %	CAR T N, %
Number of infection (%)	55	69	70
Cumulative Incidence	4.7%	7.8%	12.7%
Median time to infections (days)	30	54	42
Severity of infection Severe Non-Severe	 5 (9%) 55 (91%)	 8 (12%) 61 (88%)	 8 (11%) 62 (86%)
Risk periods 0-30 31-90	 29 (15.0%) 26 (13.4%)	 16 (8.3%) 53 (27.3%)	 27 (14.0%) 43 (22.2%)
RVI Origin Community acquired Hospital acquired	 43 (78%) 12 (22%)	 61 (88%) 8 (12%)	 53 (76%) 17 (24%)

Figure 1: Distribution of different respiratory viruses by month over the study period.

Figure 2: The figure highlights the impact of different variables associated with Respiratory Viral Infections on clinical outcomes among hematopoietic cellular therapy (HCT) and chimeric antigen receptor T-cell (CAR-T) therapy recipients in the post covid-19 pandemia era. Figure 2a: Probability of survival among patients with early vs. late onset Respiratory Viral Infections after HCT and CAR T-cell therapy. Figure 2b: Probability of survival among patients with covid-19 vs. other Respiratory Viral Infections after HCT and CAR T-cell therapy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10
15
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2022_02
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2022_04
2022_05
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2022_09
2022_10
2022_11
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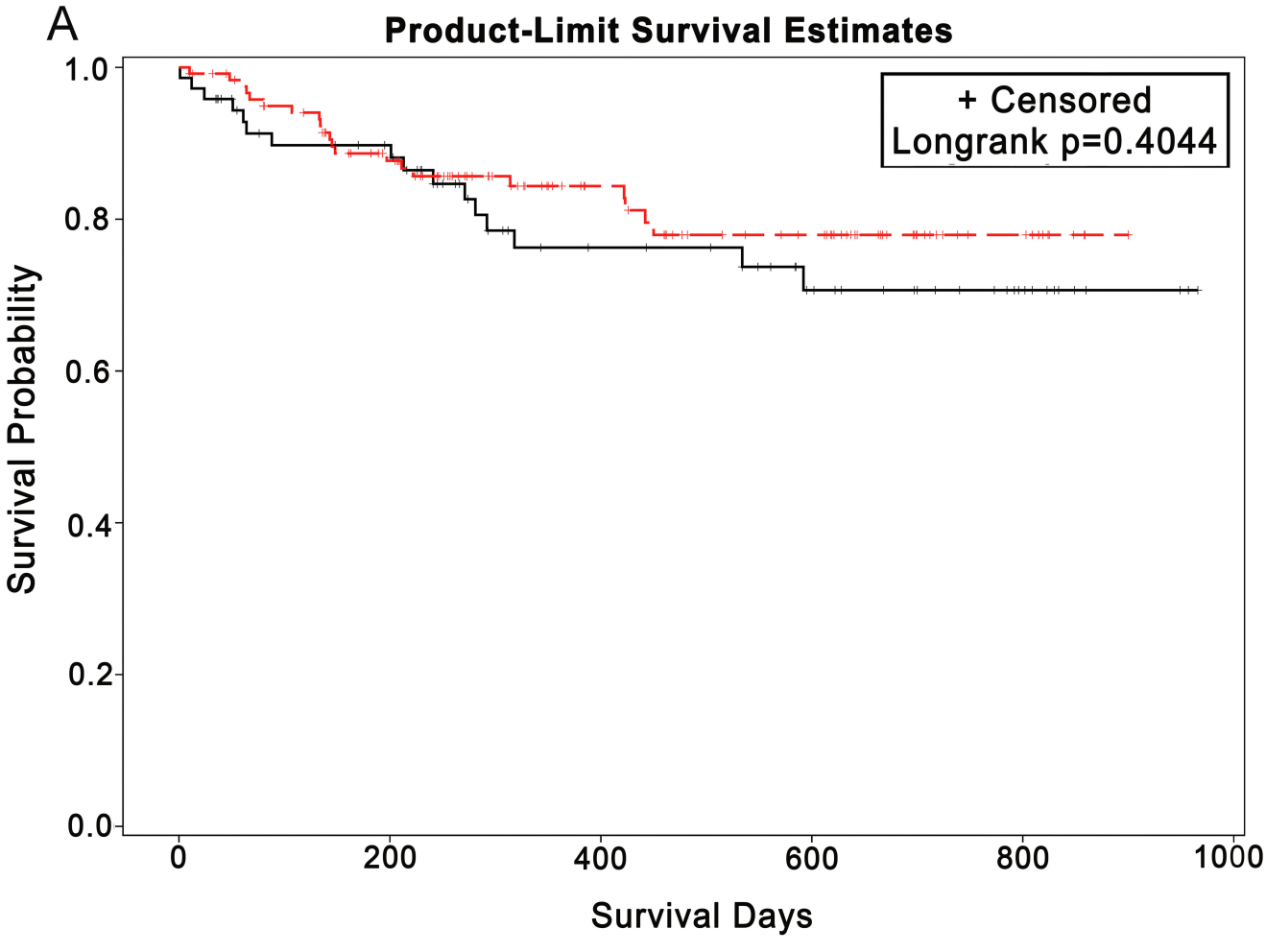
2024_04
2024_05
2024_06
2024_07
2024_08
2024_09
YEAR_MONTH
COVID-19
ADENOVIRUS
HMPV
INFLUENZA
PIV
RSV

A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+ Censored
Longrank p=0.4044
Survival Probability
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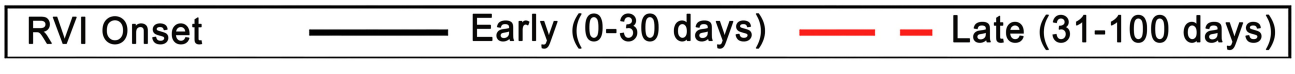
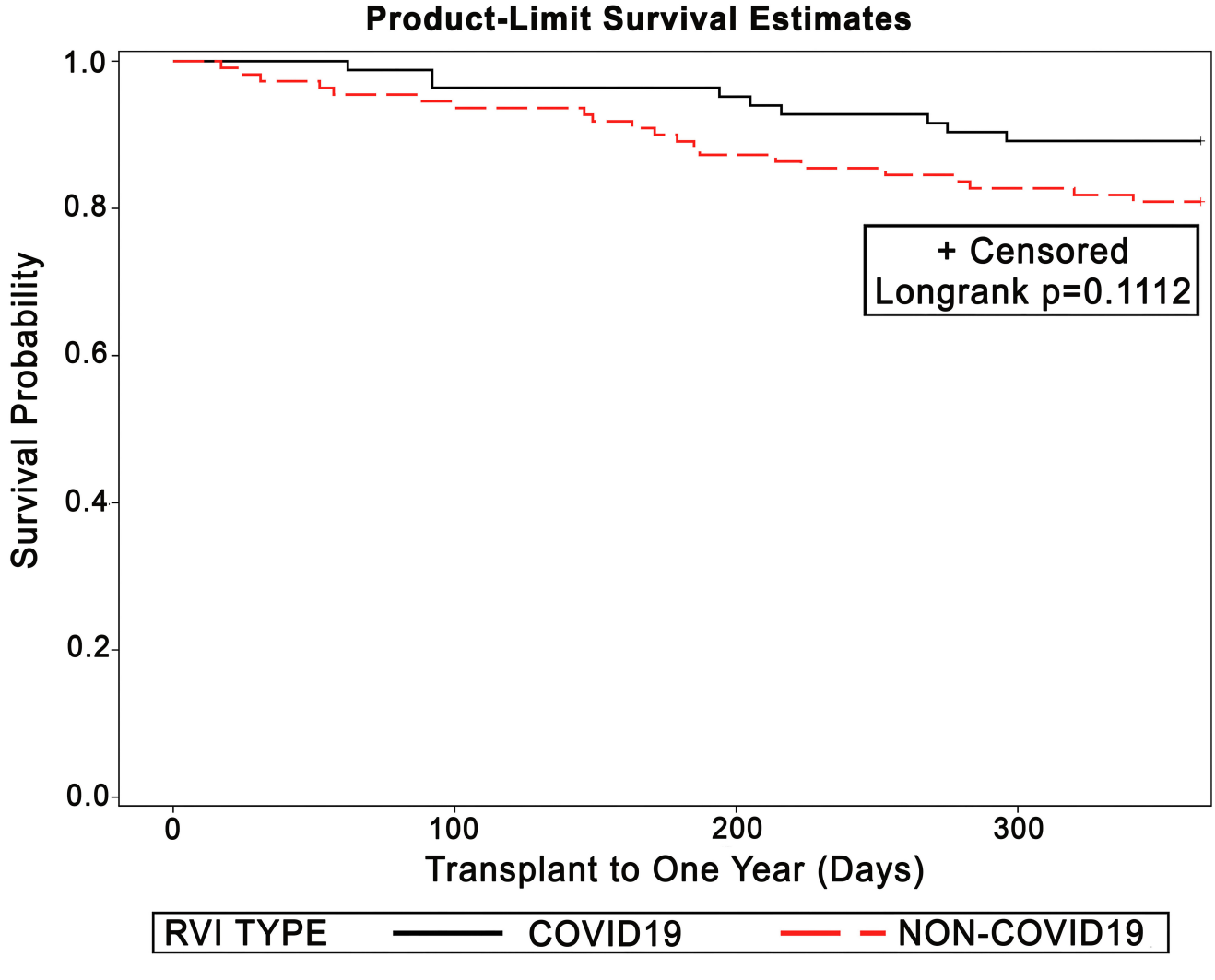
0.6
0.4
0.2
0.0
0
200
400
600
800
1000
Survival Days

B


RVI Onset
Early (0-30 days)
Late (31-100 days)


Product-Limit Survival Estimates
+ Censored
Longrank p=0.1112
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
Transplant to One Year (Days)
RVI TYPE
COVID19
NON-COVID19

Supplemental Materials:

Supplemental Table 1: Patients Characteristics for Chimeric Antigen Receptor T cell and Allogeneic HCT Cohort

CAR-T Cohort: N= 70	
Cytokine Release Syndrome (CRS)	
Y	20 (28.6)
N	3 (4.3)
Missing	47 (67.1)
Target Antigen	
BCMA	31 (45.6)
CD19	39 (51.5)
Allo Cohort details N= 69	
Conditioning Regimen Allo Cohort	
Myeloablative	23 (35.4)
Non-Myeloablative	42 (64.6)
Missing	4 (5.8)
Cell Source	
Bone marrow	1 (1.44)
Cord blood	6 (8.7)
Peripheral blood	62 (90.0)
All GvHD in the first 100 days	
Yes	47 (68)
No	22 (32)
GvHD at the time of RVI (for Allo patients)	
Yes	3 (4.3)
No	66 (95.7)
GvHD Prophylaxis group	
CNI	32 (46.4)
PTCY	35 (50.7)
Missing	2 (2.9)
ATG	
Rabbit ATG	2 (2.9)
None	55 (79.7)
Missing	12 (17.4)

Supplemental Table 2: Risk Factor Analysis for Severe RVIs Among Study Patients

	ALL DATA (SEVERE VS NON-SEVERE)						
	Severe n=21 episodes	**Non-Severe n=173 episodes**	**OR**	**CI (lower)**	**CI (upper)**	**p**	*
Age Group							
19 to 30	1	12	ref.				
31 to 49	5	31	1.46	0.20	10.57	0.711	
50 to 60	2	44	0.47	0.05	4.14	0.495	
>60	13	86	1.30	0.21	8.27	0.781	
Age at BMT or CART, years, median (range)							
	64.5 (25.6 - 77.3)	60.6 (19.8 - 82.3)					
Race							
Asian	4	17	2.29	0.68	7.71	0.179	
Black	3	28	1.10	0.31	3.91	0.888	
Other	1	10	1.27	0.19	8.36	0.801	
Unknown	1	7	1.78	0.25	12.54	0.561	
White	12	111	ref.				
Sex							
Female	10	74	1.22	0.50	2.98	0.664	
Male	11	99	ref.				
Underlying Malignancy							
Leukemia	7	34	1.18	0.32	4.34	0.799	
Lymphoma	5	46	0.64	0.17	2.50	0.525	
Myeloma	5	69	0.43	0.11	1.65	0.220	
Other	4	24	ref.				
Comorbidities							
Diabetes							
Y	5	29	1.63	0.57	4.69	0.363	
N	16	144	ref.				
COPD							
Y	0	8	0.45	0.02	9.64	0.612	

N	21	165	ref.				
CKD							
Y	14	80	2.25	0.88	5.72	0.090	
N	7	93	ref.				
HTN							
Y	15	117	1.15	0.43	3.04	0.783	
N	6	56	ref.				
CHF							
Y	5	21	2.36	0.80	6.97	0.119	
N	16	152	ref.				
Tocilizumab 30 days before RVI							
Y	8¶	18	5.29	1.95	14.36	0.001	*
N	13	155	ref.				
Rituximab within 6 months prior to RVI							
Y	2	21	0.91	0.22	3.76	0.896	
N	19	152	ref.				
2 or more Comorbidities							
Y	14	83	2.10	0.82	5.34	0.121	
N	7	90	ref.				
Smoking Status							
Current	**2**	**18**	**0.94**	**0.22**	**4.02**	**0.930**	
Former	4	45	0.69	0.23	2.09	0.507	
Never	15	107	ref.				
ANC (+/-7 days of RVI onset)							
ANC>=500 cells/mcL	12	150	0.20	0.08	0.52	0.001	*
ANC<500 cells/mcL	9	22	ref.				
ALC(+/-7 days of RVI onset)							
ALC>=200 cells/mcL	4	122	0.11	0.04	0.32	<.0001	*
ALC<200 cells/mcL	17	50	ref.				
Creatinine							

Creatinine>=1.1 mg/dL	6	47	1.12	0.42	2.98	0.826	
Creatinine<1.1 mg/dL	15	126	ref.				
Hypogammaglobulinemia							
IgG>=400 mg/dL	9	79	0.66	0.23	1.87	0.434	
IgG<400 mg/dL	7	41	ref.				
KPS category							
Below 90	6	75	0.67	0.21	2.12	0.494	
90 and Above	6	50	ref.				
Virus Type							
Influenza Y	0	10	0.36	0.02	7.34	0.508	
Influenza N	21	163	ref.				
PIV Y	9	32	3.31	1.30	8.42	0.012	*
PIV N	12	141	ref.				
RSV Y	4	28	1.31	0.43	4.05	0.636	
RSV N	17	145	ref.				
COVID-19 Y	2	82	0.14	0.04	0.55	0.005	*
COVID-19 N	19	91	ref.				
HMPV Y	0	12	0.30	0.02	5.90	0.429	
HMPV N	21	161	ref.				
Adenovirus Y	6	9	7.26	2.29	23.06	0.001	*
Adenovirus N	15	164	ref.				
Antiviral use							
Yes	6	66	0.68	0.26	1.79	0.433	
No	15	107	ref.				
Transplant Type							
ALLO	8	61	ref.				
AUTO	5	50	0.79	0.25	2.5	0.683	
CAR-T	8	62	0.98	0.35	2.7	0.975	
Transplant to RVI (Days)							
Early (within 0-30 days)	14	58	ref.				

Late (within 31-100 days)	7	115	0.26	0.10	0.7	0.005	*
Steroid Use 14 Days before RVI							
Yes	14	53	4.32	1.70	11.2	0.002	*
No	7	120	ref.				

¶ 6 CAR T cell therapy recipients, 2 Allogeneic HCT recipients

Supplemental Table 3. Univariate Analysis for Risk Factor Assessment for Severe RVIs Among Allogeneic HCT Recipients

	ALLO TRANSPLANTS (SEVERE VS NON-SEVERE)						
	Severe (Type 4) n=8 episodes	**Non-Severe (Types 0-3) n=61 episodes**	**OR**	**CI (lower)**	**CI (upper)**	**p**	*****
Age Group							
19 to 30	1	6	ref.				
31 to 49	3	13	1.12	0.12	10.68	0.919	
50 to 60	0	13	0.16	0.01	5.27	0.305	
>60	4	29	0.66	0.08	5.67	0.706	
Age at Transplant, median (range)							
	57.2 (25.6 - 77.3)	59.3 (25.7 - 82.3)					
Days from Transplant to RVI, median							
	19.5	56.0					
Race							
Asian	1	4	2.76	0.30	25.21	0.369	
Black	1	5	2.26	0.26	19.27	0.457	
Other	0	3	1.18	0.03	40.58	0.926	
Unknown	1	4	2.76	0.30	25.21	0.369	
White	5	45	ref.				
Sex							
Female	3	27	0.76	0.17	3.45	0.717	
Male	5	34	ref.				
Underlying Cancer							
Leukemia MDS	5	53	0.03	<0.001	3.45	0.152	
Lymphoma	2	7	0.11	<0.001	13.13	0.367	
Myeloma	0	1	0.13	<0.001	68.95	0.518	
Other	1	0	ref.				
HCT-CI Comorbity Index							
Low (<2)	0	20	ref.				
Med (btwn 2-4)	4	30	6.05	0.29	127.25	0.078	
High (>4)	4	11	16.05	0.73	352.02	0.247	
KPS							
70	0	5	ref.				
80	1	20	0.81	0.02	29.36	0.906	
90	5	29	2.05	0.07	55.78	0.670	
100	0	1	3.69	0.02	922.09	0.643	

KPS category							
Below 90	1	25	0.24	0.03	2.19	0.152	
90 and Above	5	30	ref.				
HLA- Match_Grouped							
Unrelated matched	1	21	0.27	0.04	1.84	0.183	
Related haploidentical	0	5	0.36	0.01	9.57	0.539	
Related matched	1	10	0.56	0.08	4.10	0.568	
Unrelated mismatched	6	25	ref.				
HLA- Match_Cat							
Matched	2	31	ref.				
Unmatched	6	30	2.69	0.56	12.83	0.216	
Intensity							
Ablative	0	14	0.09	0.010	2.26	0.145	
Reduced Intensity	3	9	0.39	0.08	1.85	0.235	
Non-Ablative	5	38	ref.				
Antithymocyte Globulin Treatment, ATG							
Yes	0	2	1.40	0.03	61.88	0.862	
No	8	59	ref.				
D100 Acute GVHD							
Yes	5	42	0.78	0.13	0.72	0.718	
No	3	19	ref.				
D100 HIGHEST GRADE of GVHD							
1	1	3	ref.				
2	3	27	0.30	0.03	3.33	0.324	
3	1	11	0.30	0.02	4.88	0.403	
4	0	1	0.99	0.01	119.10	0.999	
D100_IBMTR_HIGHEST_GRADE_CAT							
Grade 1 or 2	4	30	ref.				
Grade 3 or 4	1	12	0.63	0.06	6.18	0.393	

Comorbidities							
Diabetes							
Y	2	9	2.13	0.40	11.31	0.377	
N	6	52	ref.				
COPD							
Y	0	4	0.75	0.03	21.34	0.867	
N	8	57	ref.				
CKD							
Y	6	29	2.87	0.60	13.70	0.187	
N	2	32	ref.				
HTN							
Y	5	43	0.67	0.15	2.92	0.592	
N	3	18	ref.				
CHF							
Y	2	9	2.13	0.40	11.31	0.377	
N	6	52	ref.				
Tocilizumab 30 days before RVI							
Y	2	1	15.50	1.31	184.31	0.030	*
N	6	60	ref.				
Rituximab within 6 months prior to RVI							
Y	0	1	2.37	0.02	232.35	0.712	
N	6	60	ref.				
2 or more Comorbidities							
Y	5	32	1.43	0.33	6.09	0.631	
N	3	29	ref.				
Smoking Status (most recent documented)							
Current	0	8	0.28	0.01	6.36	0.423	
Former	1	17	0.41	0.06	2.68	0.349	
Never	7	35	ref.				
ANC (lowest value within +/-7 days of rsv onset)							
ANC>=500 cells/mcL	5	58	ref.				
ANC<500 cells/mcL	3	3	10.64	1.17	66.1	0.011	*
ALC(lowest value within +/-7 days of rsv onset)							
ALC>=200 cells/mcL	1	48	ref.				
ALC<200 cells/mcL	7	13	18	2.74	117.62	0.003	*
Creatinine							
Creatinine>=1.1 mg/dL	2	19	0.84	0.17	4.09	0.827	

Creatinine<1.1 mg/dL	6	42	ref.				
IgG							
IgG>=400 mg/dL	3	19	0.32	0.04	2.47	0.276	
IgG<400 mg/dL	2	4	ref.				
Virus							
Influenza Y	0	3	0.983	0.03	32.48	0.992	
Influenza N	8	58	ref.				
PIV Y	3	12	2.52	0.56	11.44	0.231	
PIV N	5	29	ref.				
RSV Y	1	11	0.88	0.13	6.07	0.896	
RSV N	7	50	ref.				
COVID-19 Y	0	28	0.07	0.004	1.32	0.076	
COVID-19 N	8	33	ref.				
HMPV Y	0	4	0.75	0.03	21.34	0.867	
HMPV N	8	57	ref.				
Adenovirus Y	4	3	16.7	2.82	98.9	0.002	*
Adenovirus N	4	58	ref.				
Antiviral use							
Yes	1	23	0.33	0.05	2.11	0.240	
No	7	38	ref.				

Supplemental Table 4. Univariate Analysis for Risk Factor Assessment for Severe RVIs Among Autologous HCT Recipients

	AUTO TRANSPLANTS (SEVERE VS NON-SEVERE)						
	Severe (Type 4) n=5 episodes	**Non-Severe (Types 0-3) n=50 episodes**	**OR**	**CI (lower)**	**CI (upper)**	**p**	*****
Age Group							
19 to 30	0	2	ref.				
31 to 49	0	11	0.22	0.01	25.2	0.529	
50 to 60	2	16	0.76	0.01	39.9	0.891	
>60	3	21	0.81	0.02	40.0	0.918	
Age at Transplant, median (range)							
	62.0 (57.6 - 73.6)	58.4 (20.2 - 74.6)					
Days from Transplant to RVI, median							
	16.0	30.0					
Race							
Asian	1	3	3.25	0.29	36.5	0.340	
Black	0	18	0.21	0.01	4.6	0.316	
Other	1	3	3.25	0.29	36.5	0.340	
White	3	26	ref.				
Sex							
Female	4	23	3.51	0.49	25.0	0.210	
Male	1	27	ref.				
Underlying Cancer							
Lymphoma	2	12	2.20	0.37	13.2	0.388	
Myeloma	38	3	ref.				
HCT-CI Comorbity Index							
Low (<2)	2	17	ref.				
Med (btwn 2-4)	2	26	0.66	0.10	4.4	0.668	
High (>4)	1	7	1.40	0.14	14.0	0.775	
KPS							
70	0	9	ref.				
80	4	23	3.64	0.15	86.43	0..424	
90	1	16	1.73	0.06	54.69	0.757	

KPS category							
Below 90	4	32	1.52	0.21	11.13	0.679	
90 and above	1	16	ref.				
Comorbidities							
Diabetes							
Y	2	10	2.76	0.45	16.9	0.273	
N	3	40	ref.				
COPD							
Y	0	2	1.76	0.04	80.7	0.771	
N	5	48	ref.				
CKD							
Y	3	21	1.92	0.34	11.0	0.464	
N	2	29	ref.				
HTN							
Y	4	32	1.71	0.24	12.4	0.596	
N	1	18	ref.				
CHF							
Y	0	5	0.75	0.03	20.3	0.866	
N	5	45	ref.				
Tocilizumab 30 days before RVI							
Y	0	0	n/a				
N	5	50	ref.				
Rituximab within 6 months prior to RVI							
Y	2	4	7.38	1.00	54.4	0.050	
N	3	46	ref.				
2 or more Comorbidities							
Y	3	21	1.92	0.34	11.0	0.464	
N	2	29	ref.				
Smoking Status (most recent documented)							
Current	1	8	1.54	0.18	13.2	0.694	
Former	1	11	1.14	0.1	9.3	0.905	
Never	3	30	ref.				
ANC (lowest value within +/-7 days of rsv onset)							
ANC>=500 cells/mcL	4	49	ref.				
ANC<500 cells/mcL	1	1	11.00	0.58	207.7	0.110	
ALC(lowest value within +/-7 days of rsv onset)							

ALC>=200 cells/mcL	2	31	ref.				
ALC<200 cells/mcL	3	19	2.26	0.39	13	0.361	
Creatinine							
Creatinine>=1.1 mg/dL	3	12	4.31	0.73	25.6	0.108	
Creatinine<1.1 mg/dL	2	38	ref.				
IgG							
IgG>=400 mg/dL	1	28	0.14	0.02	1.2	0.070	
IgG<400 mg/dL	3	9	ref.				
Virus							
Influenza Y	0	2	1.76	0.04	80.7	0.771	
Influenza N	5	48	ref.				
PIV Y	3	8	7	1.12	43.7	0.037	*
PIV N	2	42	ref.				
RSV Y	2	10	0.45	16.86	0.3		
RSV N	3	40	ref.				
COVID-19 Y	0	23	0.11	0.01	2.3	0.145	
COVID-19 N	5	27	ref.				
HMPV Y	0	4	0.84	0.03	27.8	0.971	
HMPV N	5	46	ref.				
Adenovirus Y	0	3	1.23	0.04	42.4	0.907	
Adenovirus N	5	47	ref.				
Antiviral use							
Yes	2	18	1.26	0.22	7.3	0.800	
No	3	32	ref.				

Supplemental Table 5. Univariate Analysis for Risk Factor Assessment for Severe RVIs Among CAR T cell recipients

	CART TRANSPLANTS (SEVERE VS NON-SEVERE)						
	Severe (Type 4) n=8 episodes	**Non-Severe (Types 0-3) n=62 episodes**	**OR**	**CI (lower)**	**CI (upper)**	**p**	*****
Age Group							
19 to 30	0	4	ref.				
31 to 49	2	7	3.00	0.08	109.64	0.550	
50 to 60	0	15	0.29	0.00	23.04	0.580	
>60	6	36	1.60	0.06	46.81	0.784	
Age at CAR-T, median (range)							
	65.2 (32.7 - 77.3)	63.1 (19.8 - 77.1)				0.782	
Days from CAR-T to RVI, median							
	15.5 (5.5-41.5)	45.0 (20-79)				0.024	*
Race							
Asian	2	10	2.14	0.38	12.22	0.391	
Black	2	5	4.09	0.63	26.74	0.141	
Other	0	4	1.00	0.03	30.32	0.999	
Unknown	0	3	1.29	0.04	45.23	0.890	
White	4	40	ref.				
Sex							
Female	3	24	1.00	0.23	4.29	1.000	
Male	5	38	ref.				
Comorbidities							
Diabetes							
Y	1	10	1.00	0.14	7.00	1.000	
N	7	52	ref.				
COPD							
Y	0	2	1.42	0.03	62.91	0.855	
N	8	60	ref.				
CKD							
Y	5	30	1.67	0.39	7.13	0.486	
N	3	32	ref.				
HTN							
Y	6	42	1.25	0.26	6.09	0.779	
N	2	20	ref.				
CHF							
Y	3	7	4.71	0.95	23.3	0.057	

N	5	55	ref.				
Tocilizumab 30 days before RVI							
Y	6	17	6.76	1.39	32.9	0.018	*
N	2	45	ref.				
Rituximab within 6 months prior to RVI							
Y	0	16	0.17	0.01	3.31	0.239	
N	8	46	ref.				
2 or more Comorbidities							
Y	6	30	2.77	0.58	13.2	0.201	
N	2	32	ref.				
Smoking Status (most recent documented)							
Current	1	2	4.64	0.38	56.71	0.230	
Former	2	17	1.10	0.22	5.63	0.905	
Never	5	42	ref.				
ANC (lowest value within +/-7 days of rsv onset)							
ANC>=500 cells/mcL	3	43	ref.				
ANC<500 cells/mcL	5	18	3.70	0.85	16.1	0.081	
ALC(lowest value within +/-7 days of rsv onset)							
ALC>=200 cells/mcL	1	43	ref.				
ALC<200 cells/mcL	7	18	11.76	1.83	75.5	0.009	*
Creatinine							
Creatinine>=1.1 mg/dL	1	16	0.56	0.09	3.72	0.552	
Creatinine<1.1 mg/dL	7	46	ref.				
IgG							
IgG>=400 mg/dL	5	32	1.93	0.39	9.57	0.421	
IgG<400 mg/dL	2	28	ref.				
KPS category							
Below 90	1	18	0.73	0.02	29.10	0.867	
90 and Above	0	4	ref.				
Virus							
Influenza Y	0	5	0.62	0.02	15.9	0.770	
Influenza N	8	57	ref.				
PIV Y	3	12	2.57	0.57	11.7	0.221	

PIV N	5	50	ref.				
RSV Y	1	7	1.48	0.20	11.07	0.703	
RSV N	7	55	ref.				
COVID-19 Y	2	31	0.39	0.08	1.84	0.231	
COVID-19 N	6	31	ref.				
HMPV Y	0	4	0.77	0.03	21.71	0.875	
HMPV N	8	58	ref.				
Adenovirus Y	2	3	6.54	0.92	46.24	0.060	
Adenovirus N	6	59	ref.				
Antiviral use							
Yes	3	25	0.94	0.22	4.00	0.929	
No	5	37	ref.				
CAR-T PRODUCT (Target Antigen)							
BCMA	2	24	0.27	0.05	1.42	0.122	
CD19	1	24	0.16	0.02	1.15	0.068	
Other	5	14	ref.				
Cytokine Release Syndrome, Max Grade (CRS-Max)							
Grade < 2	0	13	ref.				
Grade >=2	1	10	3.86	0.13	119.24	0.441	
ICANS							
Y	0	7	0.73	0.02	24.5	0.862	
N	1	16	ref.				