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Viral Respiratory Tract Infections in Allogeneic Hematopoietic Stem Cell Transplantation Recipients in the Era of Molecular Testing

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Viral respiratory tract infection (vRTI) is a significant cause of morbidity and mortality in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). This study aimed to assess the epidemiologic characteristics, risk factors, and outcomes of vRTI occurring in the period from conditioning to 100 days after allo-HSCT in the era of molecular testing. This study was a retrospective record review of patients who underwent allo-HSCT at Royal Melbourne Hospital between January 2010 and December 2015. Symptomatic patients were tested using respiratory multiplex polymerase chain reaction (PCR). Logistic regression and Kaplan-Meier analysis were used to identify risk factors for vRTI and the risk of death or intensive care unit (ICU) admission, respectively. A total of 382 patients were reviewed, and 65 episodes of vRTI were identified in 56 patients (14.7%). Rhinovirus accounted for the majority of infections (69.2%). The majority of episodes presented initially with upper respiratory tract infection (58.5%), with 28.9% of them progressing to lower respiratory tract infection. Eleven episodes (16.9%) were associated with ICU admission. There were no deaths directly due to vRTI. Previous autologous HSCT was associated with an increased risk of vRTI (odds ratio, 2.1; 95% confidence interval, 1.0 to 4.1). The risks of death ($P = .47$) or ICU admission ($P = .65$) were not significantly different by vRTI status. vRTI is common in the first 100 days after allo-HSCT and is associated with ICU admission.

INTRODUCTION

Background

Respiratory viruses (RVs), including influenza virus, parainfluenza virus, respiratory syncytial virus (RSV), rhinovirus, coronavirus, adenovirus, and human metapneumovirus (hMPV), are common causes of viral respiratory tract infection (vRTI) [1-3]. Previous studies have shown that RVs cause significant morbidity and mortality in patients undergoing hematopoietic stem cell transplantation (HSCT), in particular allogeneic HSCT (allo-HSCT) [1-8].

The diagnosis of RVs, especially in older studies, has been dependent mainly on nonmolecular diagnostic methods, including direct antigen detection or cell culture, which are limited by poor sensitivity [9]. Molecular testing using polymerase chain reaction (PCR) allows rapid detection of RVs with high sensitivity and specificity. Moreover, multiplex assays enable the detection of multiple RVs in a single test, and these are now the current standard of care in many clinical settings. The purpose of this study was to assess the epidemiologic characteristics, risk factors, and outcomes of vRTI in allo-HSCT recipients in the era of molecular testing.

METHODS

Study Population

This study was a retrospective record review of adult patients admitted to the Bone Marrow Transplantation (BMT) unit for allo-HSCT at the Royal

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Melbourne Hospital (RMH) between January 2010 and December 2015. Only the first allo-HSCT was considered in patients who underwent multiple transplantations during the study period.

Patient records for the first 100 days following allo-HSCT were reviewed. Demographic and clinical data were collected from hospital clinical records using a case report form and included age, sex, underlying disease, previous therapy, stem cell source, conditioning therapy, graft-versus-host disease (GVHD), and outcomes (ie intensive care unit [ICU] admission and death). Baseline measurements of lymphocyte and neutrophil levels and cytomegalovirus (CMV) seropositivity were collected. Data on respiratory viral PCR testing and results from symptomatic patients were extracted from the RMH pathology database.

For patients with RV infection, the number of vRTIs, type of RVs, clinical presentation, antiviral therapy, and outcomes (ie, ICU admission, death, use of mechanical ventilation, and progression to lower respiratory tract infection [LRTI]) were also obtained during the 100-day period. During the review period, treatment of RSV with i.v. ribavirin was recommended in the setting of radiologic changes in patients within 100 days of allo-HSCT.

Microbiological Methods

All specimens, including nasal and throat swabs, nasopharyngeal aspirates, and sputum or bronchoalveolar lavage specimens, were examined by real-time PCR at the Melbourne Health Shared Pathology Service according to previously published protocols [10,11]. RVs included in the multiplex PCR panel were RSV, influenza type A and B, and rhinovirus. The testing of copathogens was not part of routine assessment and was performed at the discretion of treating physician. These tests included conventional culture for bacteria and fungi; PCR for *Legionella*, *Pneumocystis jirovecii*, and *Aspergillus* [12]; viral PCR for herpes simplex virus (HSV)-1, HSV-2, CMV, varicella zoster virus, human herpesvirus (HHV)-6, HHV-8, hMPV, and adenovirus; and bacterial PCR for *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Chlamydia psittaci*.

Definitions

Baseline measurements of lymphocytes and neutrophils were defined as measurements obtained on the day of admission ± 2 days. Lymphopenia was defined as an absolute lymphocyte count below 1.0×10^9/L, and neutropenia was defined as absolute neutrophil count below 2.0×10^9/L. Conditioning intensity was defined in accordance with Center for International Blood and Marrow Transplant Research guidelines [13]. Upper respiratory tract infection (URTI) was defined as an RV detected in an upper respiratory tract fluid specimen together with symptoms and/or signs, with the exclusion of other possible causes. LRTI was defined as detection of RV in respiratory secretions, preferentially in samples obtained from sites of involvement together with pathological sputum production, hypoxia, or pulmonary infiltrates [14]. Progression to LRTI was defined as the onset of LRTI in patients with a previous URTI. An episode of infection was defined as evidence of RV, URTI, or LRTI detected during the conditioning period and for up to 100 days following allo-HSCT. An infection was considered subsequent if the RV detected was nonidentical or if it was identified at least 30 days following the previous episode with the identical RV [15]. The presence of a copathogen was defined as a bacterial, fungal, or nonrespiratory virus pathogen isolated from a respiratory tract sample during an episode of infection. Overall mortality was defined as death due to any cause within 100 days of vRTI diagnosis or allo-HSCT. Death attributable to vRTI was defined as death resulting from respiratory failure with other causes excluded.

Statistical Methods

The risk of vRTI was calculated as the number of patients testing positive for any RV among all allo-HSCT recipients. Patients' baseline characteristics were compared by vRTI status using the chi-square test or Fisher exact test for categorical variables and the Student *t* test or Wilcoxon rank-sum test for continuous variables.

Only the first episode of vRTI was considered for risk factor analysis. Univariable and multivariable analyses of risk factors for vRTI were performed using logistic regression models. Variables with a *P* value <.1 were included in the multivariable testing, along with variables previously identified as important risk factors for vRTI, including lymphopenia, GVHD, and donor relation [8,16,17].

Patients with vRTI had their records reviewed for 100 days following infection. In patients without vRTI, the review was censored to the date of death/ICU admission or 100 days following transplantation, whichever was sooner. Survival (to death or ICU admission) within 100 days following transplantation was assessed using Kaplan-Meier plots, stratified by vRTI status. The log-rank test was used to assess differences in survival among groups. All statistical analyses were performed using R version 3.3.1, with statistical significance defined at $\alpha = .05$.

Ethics

Approval to conduct the study was granted by the Melbourne Health Human Research Ethics Committee (reference QA2017024).

RESULTS

Patient Characteristics

A total of 386 patients were identified during the review period (January 2010 to December 2015). Medical records could not be obtained for 4 patients, including 1 patient with vRTI (Figure 1). The 382 patients reviewed included slightly more males (n = 222; 58.1%) than females (n = 160; 41.9%), and the median patient age was 47 years (interquartile range [IQR], 36 to 56 years). The median age of patients with vRTI was significantly lower than patients without ($P = .03$). Other patient demographic data and characteristics were not significantly different by vRTI status (Table 1).

Prevalence of vRTI

Out of 382 patients, 222 were tested for vRTI (58.1%) within 100 days following allo-HSCT and 65 episodes of vRTI were identified in 56 patients (14.7%). Eight patients had multiple episodes, 7 with 2 episodes and 1 with 3 episodes. The median time to onset of the first infection from the date of allo-HSCT was 41 days (IQR, 9.8 to 64.0 days). Among the 56 patients identified with vRTI, their first episode was identified during the first 30 days following transplantation in 23 (41.1%). The clinical characteristics of vRTI episodes are summarized in Table 2.

Rhinovirus accounted for the majority of infection episodes (45 of 65; 69.2%), followed by RSV (11 of 65; 16.9%), and there was 1 episode of coinfection with these 2 pathogens. Most of the cases initially presented with URTI (38 of 65; 58.5%), and this was most pronounced for RSV (8 of 11; 72.7%). Progression to LRTI was observed in 28.9% (11 of 38) of all patients with an initial presentation of URTI and was most common for rhinovirus (8 of 25; 32.0%).

The most common symptom observed was cough (n = 51; 78.5%), followed by fever (26; 40.0%), coryza (23; 35.4%), and sputum production (19; 29.2%). The rates of cough (100% versus 68.4%), sputum production (76.0% versus 0%), and fever (60.0% versus 29.0%) were significantly higher in the patients with LRTI compared with those with URTI (all $P < .05$). Antiviral therapy was administered in 14 cases (21.5%). Among the 11 patients with RSV, 3 (27.3%; 1 URTI and 2 LRTI) received ribavirin, and 1 (9.1%; URTI) received either placebo or gs-5806 as part of a clinical trial. All 9 patients who had either influenza A or B received oseltamivir, and 1 patient with an LRTI with rhinovirus infection (n = 1/45, 2.2%) received i.v. immunoglobulin. Antiviral therapy was initiated within a median of 2.0 days (IQR, 1.0 to 2.8 days) after the detection of RV. The median duration of antiviral therapy was 5.5 days (IQR, 4.0 to 8.8 days).

Sixteen copathogens were identified from 10 vRTI episodes (15.4%). One episode had 4 copathogens (3 bacterial and 1 fungal), and 3 episodes had 2 copathogens (2 episodes with 2 fungal pathogens and 1 episode with a bacterial and a fungal pathogen). Bacterial copathogens were found in 8 out of 10 episodes (80.0%) and accounted for one-half the copathogens detected (8 of 16; 50.0%). These included *Staphylococcus* spp. (n = 3), *Enterococcus faecium* (n = 2), *Haemophilus influenzae* (n = 1), *Chlamydophila pneumoniae* (n = 1), and *Pseudomonas aeruginosa* (n = 1). Of note, fungal and nonrespiratory virus copathogens were only found concomitantly with rhinovirus infection. Fungal copathogens identified include *Aspergillus* (n = 2), *Candida albicans* (n = 1), *Cladosporium* sp.

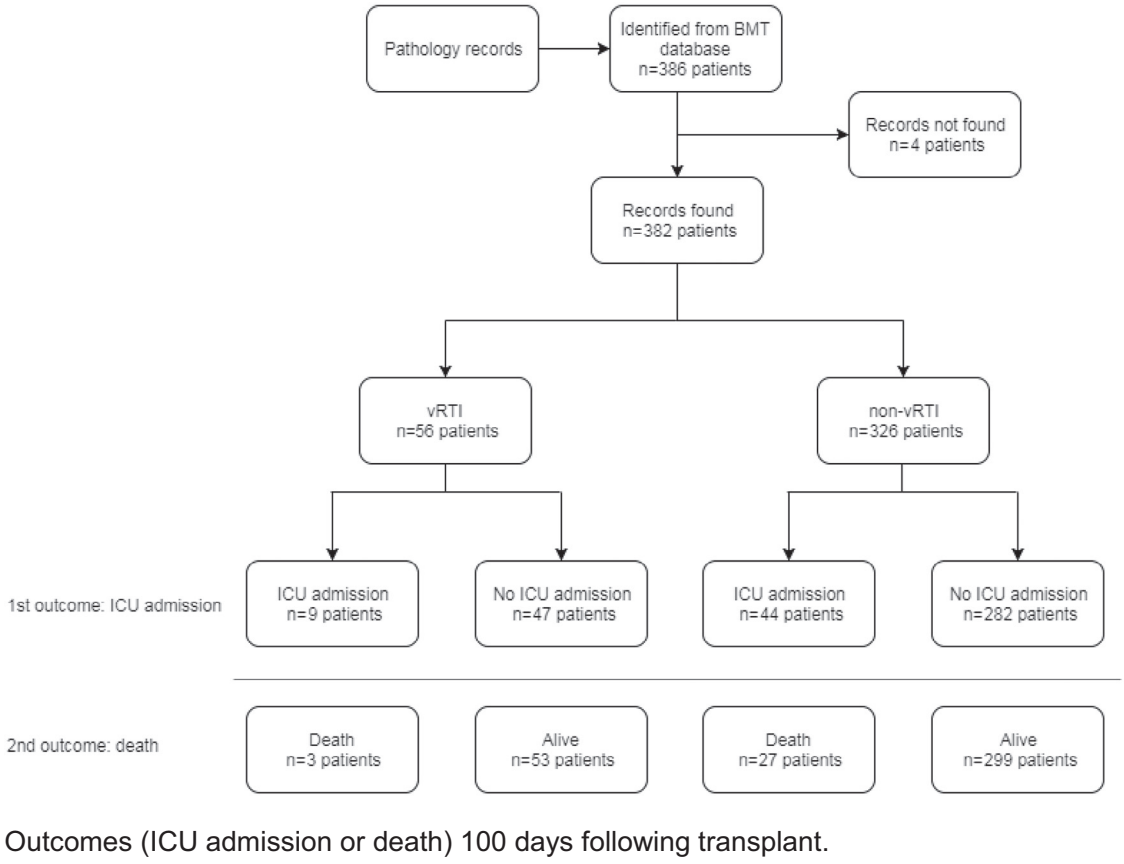

Figure 1. Flow chart diagram of patients included in the study.

(n = 1), *Saccharomyces cervisiae* (n = 1), and *P. jirovecii* (n = 1). No episodes met the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria for invasive fungal disease. The nonrespiratory viruses isolated were CMV and HHV-6.

Risk Factors for vRTI

In univariate and multivariable analyses, only previous autologous HSCT was associated with increased risk of vRTI (odds ratio, 2.1; 95% confidence interval, 1.0 to 4.1). Other variables, including age, sex, underlying disease, CMV seropositivity, donor relation, stem cell source, conditioning regimen and intensity, acute GVHD, lymphopenia, and neutropenia were not statistically significant (Table 3). In addition, no variables were significantly associated with the risk for vRTI for fixed periods following HSCT (<30 days, 30 to 60 days, or 61 to 100 days following transplantation).

Outcomes of vRTI

There were a total of 65 episodes of vRTI in our study cohort. During the study period, 11 episodes (16.9%) were associated with ICU admission within 100 days of vRTI, with 9 episodes (13.8%) necessitating the use of mechanical ventilation. Of the 11 episodes, 5 episodes of vRTI (2 rhinovirus, 2 RSV, and 1 influenza A) had LRTI as the initial presentation and respiratory symptoms that precipitated the ICU admission. Patients were admitted to ICU within a median of 6.0 days (IQR, 0 to 15.5 days) after vRTI and for a median duration of 9 days (IQR, 5.5 to 12.5 days). The risk of ICU admission within 100 days following transplantation between patients with vRTI (9 of 56; 16.0%) and those without vRTI (44 of 326; 13.5%) was not significantly different ($P = .65$) (Figure 2).

Five patients died within 100 days of vRTI, all of whom had rhinovirus infection and prior ICU admission. Three patients were admitted to the ICU 1 day before the detection of rhinovirus, whereas the other 2 patients had ICU admission on day 22 and day 38 following the detection of rhinovirus. Of the 5 patients who died, 4 (80.0%) had LRTI as the initial site of infection and 3 (60.0%) had copathogens detected. However, none of these deaths was directly attributable to vRTI. Causes of death included multiorgan failure (n = 2), pneumonitis (n = 1), acute pulmonary edema (n = 1), and aspiration pneumonia, GVHD, and fluid overload (n = 1). The risk of mortality within 100 days following transplantation between patients with vRTI (3 of 56; 5.4%) and those without vRTI (27 of 326; 8.3%) was not significantly different ($P = .47$) (Figure 2). All vRTI patients who died within 100 days following transplantation developed vRTI during the first 30 days following transplantation.

DISCUSSION

In this study, vRTI was prevalent among allo-HSCT recipients during the first 100 days following transplantation. The frequency of vRTI among allo-HSCT recipients was 14.6%, which is consistent with the rates of 3.5% to 29% reported elsewhere [2,3,6,7]. However, differences between our study and previous studies include a shorter duration of review (100 days), inclusion of symptomatic patients only, and the range of pathogens tested [2,3,6,7,17].

Table 1
Characteristics of Allo-HSCT Recipients with and without vRTI

Variable	vRTI	Non-vRTI	*P* Value
Number of patients (%)	56 (14.7)	326 (85.3)	
Age, yr, median (range)	41.9 (18.7-61.5)	47.5 (17.0-69.6)	.03*
Sex, n (%)			.25
Female	19 (33.9)	141 (43.3)	
Male	37 (66.1)	185 (56.7)	
Underlying disease, n (%)			.71†
Malignant	55 (98.2)	312 (95.7)	
AML	7 (12.5)	40 (12.3)	
ALL	18 (32.1)	137 (42.0)	
NHL	5 (8.9)	28 (8.6)	
MDS	6 (10.7)	36 (11.0)	
Other	19 (33.9)	69 (21.7)	
Nonmalignant	1 (1.8)	14 (4.3)	
SAA	1 (1.8)	6 (1.8)	
Other	0 (0.0)	8 (2.5)	
CMV seropositivity, n (%)	37 (66.1)	191 (58.6)	.47
Donor relation, n (%)			.69
Related	30 (53.6)	153 (46.9)	
Cord	4 (7.1)	25 (7.7)	
Unrelated	22 (39.3)	148 (45.4)	
Stem cell source, n (%)			.92
Bone marrow	5 (8.9)	38 (11.7)	
Peripheral blood	47 (83.9)	263 (80.7)	
Umbilical cord blood	4 (7.1)	25 (7.7)	
Conditioning regimen, n (%)			
Radiotherapy-based	16 (28.6)	82 (25.2)	.71
Chemotherapy only	40 (71.4)	244 (74.8)	.71
Conditioning intensity, n (%)			.52
Myeloablative	28 (50.0)	161 (49.4)	
Nonmyeloablative	11 (19.6)	43 (13.2)	
Reduced intensity	17 (30.4)	119 (36.5)	
T cell depletion, n (%)	22 (39.3)	140 (42.9)	.71
Acute GVHD, n (%)	28 (50.0)	151 (46.3)	.72
Grade I	13 (46.4)	64 (42.4)	
Grade II	10 (35.7)	54 (35.8)	
Grade II	4 (14.3)	22 (14.6)	
Grade IV	1 (3.6)	11 (7.3)	

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; SAA, severe aplastic anemia.

* *P* value calculated using the Wilcoxon rank-sum test.

† *P* value calculated using the χ^2 test comparing categories (malignant versus nonmalignant).

Rhinovirus accounted for the majority of infections, as has been reported previously, albeit among symptomatic and asymptomatic patients [2,17]. Copathogens were identified in 15% of the episodes and were most common in patients with rhinovirus infection. Ison et al. [18] hypothesized that rhinovirus might predispose patients to additional infection. Respiratory colonization with potentially pathogenic bacteria also may increase the risk of subsequent vRTI [19]. However, we note that in both that study and our present study, the number of patients was small, and further investigation of a potential link is warranted.

In our cohort, patients who had undergone previous auto-HSCT were at increased risk of developing vRTI independent of GVHD, donor relation, and lymphopenia. Auto-HSCT has been identified as an important risk factor for progression to LRTI [8]. Previous auto-HSCT may reflect advanced disease status and thus the susceptibility of patients to vRTI. In addition, cumulative immune suppression from multiple lines of previous therapy may increase the risk of vRTI, as has been seen in patients with multiple myeloma [15]. Delays in immune recovery following auto-HSCT also could explain the increased risk of vRTI in this patient population [20,21].

A key findings of the present study was the low number of deaths in patients with vRTI, with no mortality directly attributable to vRTI. This finding was consistent with rates reported in previous studies (0% to 4.7%) [3,8,22,23]. We were unable to directly assess factors contributing to reduced mortality, but postulate that it may be attributable to high standards of supportive care. In addition, antiviral therapy was initiated in some RSV cases and in all episodes of influenza type A and B infection early in the course of infection. Among the patients with vRTI, all deaths occurred in patients who acquired the infection within 30 days of transplantation. This high risk and poor prognosis subgroup supports the need for strict infection prevention measures for staff and patients in the early days after transplantation [17,23-27], along with careful assessment of patients presenting for allo-HSCT with respiratory symptoms.

Our study demonstrates that vRTI is an important cause of morbidity in allo-HSCT recipients. Up to 17% of vRTI episodes necessitated ICU admission and 14% required the use of mechanical ventilation, percentages consistent with previous reports [24-26]. Overall, close to 40% of patients had LRTI on initial presentation. Progression to LRTI occurred in 31% of infections, most commonly involving rhinovirus. Progression to LRTI was also observed in 25% of RSV URTI episodes, a higher rate than reported previously [28]. Both the innate and adaptive arms of the immune system, particularly neutrophils and cytotoxic T cells, play integral roles in the defense against vRTI [19]. Th1-dominant responses,

Table 2
Clinical Characteristics of vRTI and Outcomes by Viral Pathogen

Variable	RSV	Influenza A	Influenza B	Rhinovirus
Number of episodes (%)	11 (16.9)*	7 (10.8)	2 (3.1)	45 (69.2)
Number of patients (%)	10 (17.9)	3 (5.4)	2 (3.6)	41 (73.2)
Initial site of presentation, n/N (%)				
URTI	8/11 (72.7)	4/7 (57.1)	1/2 (50.0)	25/45 (55.6)†
LRTI	3/11 (27.3)	3/7 (42.9)	1/2 (50.0)	18/45 (40.0)†
Progression to LRTI (from URTI), n/N (%)	2/8 (25.0)	1/4 (25.0)	0 (0.0)	8/25 (32.0)
Symptoms, n/N (%)				
Fever	3/11 (27.3)	6/7 (85.7)	2/2 (100)	15/45 (33.3)
Shortness of breath	0 (0.0)	0 (0.0)	0 (0.0)	3/45 (6.7)
Cough	10/11 (90.9)	6/7 (85.7)	2/2 (100)	33/45 (73.3)
Sputum	2/11 (18.2)	2/7 (28.6)	1/2 (50.0)	14/45 (31.1)
Coryza	4/11 (36.4)	3/7 (42.9)	0 (0.0)	16/45 (35.6)
Antiviral therapy, n/N (%)	4/11 (36.4)	7/7 (100)	2/2 (100)	1/45 (2.2)
Presence of copathogen, n/N (%)	1/11 (9.1)	1/7 (14.3)	0 (0.0)	8/45 (17.8)
Bacterial	1/11 (9.1)	1/7 (14.3)	0 (0.0)	6/45 (13.3)
Fungal	0 (0.0)	0 (0.0)	0 (0.0)	6/45 (13.3)
Viral	0 (0.0)	0 (0.0)	0 (0.0)	2/45 (4.4)
Outcomes, n/N (%)				
ICU admission	3/11 (27.3)	1/7 (14.3)	0 (0.0)	7/45 (15.6)
Use of mechanical ventilation	1/11 (9.1)	1/7 (14.3)	0 (0.0)	7/45 (15.6)
Nonattributable death‡	0 (0.0)	0 (0.0)	0 (0.0)	5/41 (12.2)

* Includes 1 episode in which both RSV and rhinovirus were detected concurrently.
† Percentages do not sum to 100 because 2 episodes of rhinovirus infection were identified as neither URTI nor LRTI, because there was insufficient information available for classification.
‡ Nonattributable death was calculated using the number of patients.

Table 3
Univariate and Multivariate Logistic Regression Analysis of Risk Factors for vRTI

Variable	Category	vRTI, n	Non-vRTI, n	Univariable			Multivariable		
				OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age, yr	<50	37	184	1.00					
	≥50	19	142	.67	.36-1.19	.18			
Sex	Female	19	141	1.00					
	Male	37	185	1.48	.83-2.74	.19			
Underlying disease	Malignant	55	312	1.00					
	Nonmalignant	1	14	.41	.02-2.08	.39			
CMV status	Negative	19	134	1.00					
	Positive	37	191	1.37	.76-2.52	.30			
Donor relation	Related	30	153	1.00					
	Cord	4	25	.82	.23-2.29	.72	.79	.21-2.35	.69
	Unrelated	22	148	.76	.41-1.37	.36	.79	.42-1.47	.46
Stem cell source	Bone marrow	5	38	1.00					
	Peripheral blood	47	263	1.36	.55-4.10	.54			
	Umbilical cord	4	25	1.22	.28-5.03	.79			
Radiotherapy-based conditioning	No	40	244	1.00					
	Yes	16	82	1.19	.62-2.20	.59			
Chemotherapy-only conditioning	No	16	82	1.00					
	Yes	40	244	.84	.45-1.62	.59			
Conditioning intensity	Myeloablative	28	161	1.00					
	Non-myeloablative	11	43	1.47	.66-3.13	.33			
	Reduced intensity	17	119	.82	.42-1.56	.55			
T cell depletion	No	35	186	1.00					
	Yes	21	132	.86	.48-1.53	.61			
Acute GVHD	No	28	175	1.00					
	Yes	28	151	1.16	.66-2.05	.61	1.10	.61-2.00	.75
Acute GVHD grade	1	13	64	1.00					
	2	10	54	.91	.36-2.24	.84			
	3	4	22	.90	.23-2.84	.86			
	4	1	11	.45	.02-2.62	.46			
Lymphopenia	No	29	160	1.00					
	Yes	24	151	.88	.49-1.57	.66	.89	.48-1.62	.70
Neutropenia	No	36	199	1.00					
	Yes	17	112	.84	.44-1.54	.58			
Previous autograft	No	42	281	1.00					
	Yes	14	45	2.08	1.03-4.05	**.04**	2.14	1.05-4.20	**.03**
Previous allograft	No	55	319	1.00					
	Yes	1	7	.83	.04-4.78	.86			

Boldfaced values indicate significance.
CI indicates confidence interval; OR, odds ratio.

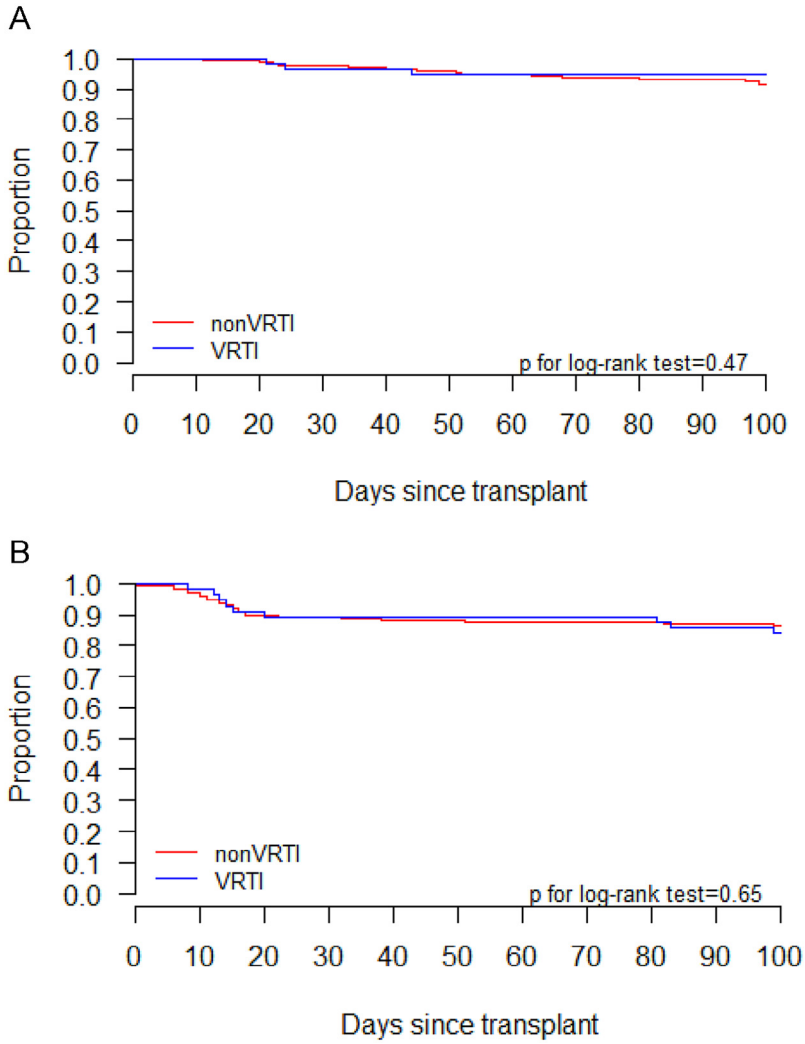

Figure 2. Kaplan-Meier curves showing the probability of survival by vRTI status. The log-rank test was used to assess differences in the survival to death (A) and ICU admission (B) among 382 patients within 100 days after transplantation.

mediated by IFN-γ, appear to have a protective role in RSV infections, whereas Th2 responses may be associated with more severe disease manifestations [29]. The profound immune depletion and impaired immune responses seen in the acute period following transplantation could account for the rates of initial LRTI and progression seen even with respiratory viruses considered less pathogenic, such as rhinoviruses. In addition, our cohort had a lower rate of antiviral therapy for RSV. Because we did not evaluate pulmonary function test results, the risk for vRTI and later complications, such as airway disease, as shown previously by Erard et al. [30], could not be assessed.

A limitation of this study was the number of RVs included in the multiplex PCR panel. Other RVs, such as parainfluenza virus, adenovirus, coronavirus, and hMPV, were not routinely tested but might be important causes of morbidity in these patients. As such, rhinovirus as a cause of vRTI and its burden in the study may be overestimated. Furthermore, because in this study we examined only prevalence, risk factors, and outcomes of vRTI within 100 days following transplantation our results might be not translatable beyond this time frame. However, because this is a known high-risk period [23,31], our study focused on this time frame to highlight the importance of early preventive measures and infection control measures among patients as well as healthcare workers following transplantation.

In conclusion, vRTI was prevalent among our allo-HSCT recipients. Although its impact on mortality appears limited, it led to a number of ICU admissions and necessitated the use of mechanical ventilation in several cases. Our findings indicate that an association between previous auto-HSCT and an increased risk of vRTI. Outcomes were poorest for patients diagnosed within 30 days following transplantation, a group of patients at high risk and with a poor prognosis for whom early preventive and infection control measures should be targeted.

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