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Lower Respiratory Tract Diseases Caused by Common Respiratory Viruses among Stem Cell Transplantation Recipients: A Single Center Experience in Korea

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Purpose: To describe the incidence, clinical courses, and risk factors for mortality of lower respiratory tract diseases (LRDs) caused by common respiratory viruses (CRVs) in stem cell transplantation (SCT) recipients.

Materials and Methods: We retrospectively reviewed the medical records of 1038 patients who received SCT between January 2007 and August 2011 at a single center in Korea.

Results: Seventy-one CRV-LRDs were identified in 67 (6.5%) patients. The human parainfluenza virus (HPIV) was the most common causative pathogen of CRV-LRDs at 100 days [cumulative incidence estimate, 23.5%; 95% confidence interval (CI), 3.3–43.7] and 1 year (cumulative incidence estimate, 69.2%; 95% CI, 45.9–92.5) following SCT. The 30-day overall mortality rates due to influenza-LRDs, respiratory syncytial virus-LRDs, HPIV-LRDs, and human rhinovirus-LRDs were 35.7, 25.8, 31.6, and 42.8%, respectively. Co-pathogens in respiratory specimens were detected in 23 (33.8%) patients. The overall mortality at day 30 after CRV-LRD diagnosis was 32.8% (22/67). High-dose steroid usage (p=0.025), a severe state of immunodeficiency (p=0.033), and lymphopenia (p=0.006) were significantly associated with death within 30 days following CRV-LRD diagnosis in a univariate analysis. Multivariate logistic regression analysis revealed that high-dose steroid usage [odds ratio (OR), 4.05; 95% CI, 1.12–14.61; p=0.033] and lymphopenia (OR, 6.57; 95% CI, 1.80–24.03; p=0.004) were independent risk factors for mortality within 30 days of CRV-LRDs.

Conclusion: CRV-LRDs among SCT recipients showed substantially high morbidity and mortality rates. Therefore, the implement of an active diagnostic approaches for CRV infections is required for SCT recipients with respiratory symptoms, especially those receiving high-dose steroids or with lymphopenia.

Key Words: Hematopoietic stem cell transplantation, human parainfluenza virus, influenza virus, respiratory syncytial virus, rhinovirus

INTRODUCTION

Annually, more than 50000 individuals receive hematopoietic stem cell transplantations (SCTs) worldwide. SCT recipients are at higher risk of severe infections, since they often remain in a state of immunosuppression after transplantation, depending on such comorbidities as graft-versus-host disease (GVHD) and the need for immunosuppressive drug treatment.[1,2] In particular, SCT recipients are susceptible to common respiratory viruses (CRVs) owing to their impaired T-cell immunity.[3] CRVs are common causes of both upper respiratory tract disease

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(URD) and lower respiratory tract disease (LRD) in this population, and have been associated with significant morbidity and mortality.[4-6] To date, there has been only a preliminary study of infections caused by CRVs among SCT recipients in Korea.[7,8] However, the epidemiology of individual CRVs varies according to the region and the times and many advances in the diagnosis and treatment of infections caused by CRVs have been achieved. The present study aimed to describe the incidence, clinical courses, and risk factors for mortality associated with LRDs caused by CRVs in SCT recipients at a single SCT center in Korea.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the medical records of 1038 patients aged ≥18 years who had undergone a SCT between January 1, 2007 and August 31, 2011 at the Catholic Blood and Marrow Transplantation Centre of Seoul St. Mary's Hospital, The Catholic University of Korea (Seoul, Republic of Korea). The aim was to identify LRDs caused by CRVs. CRVs associated with LRDs in patients included influenza A and B viruses, respiratory syncytial virus (RSV), human parainfluenza virus (HPIV) 1–3, human rhinovirus (HRhV), human adenovirus (HAdV), and human metapneumovirus (HMPV). Clinical information, including demographics, comorbidities, coinfections, and mortality were investigated. The endpoint of the study was set as January 31, 2012, or the time of death or loss to follow up. This study was approved by the Institutional Review Board of the Yeouido and Seoul St. Mary's Hospital (approval nos. SC10RISI0023 and KC13RISI0364).

Respiratory virus identification

SCT recipients with respiratory symptoms were screened for CRVs at the discretion of physicians. Specimens for diagnostic testing included nasal or throat swabs, sputum, tracheal aspirates, bronchial wash fluid, and bronchoalveolar lavage (BAL) fluid. Laboratory tests to identify CRVs included the respiratory virus polymerase chain reaction (PCR) multiplex panel (AdvanSure RV Real-Time PCR Kit; LG Life Sciences, Seoul, Korea) and rapid influenza antigen testing (BD Veritor System for Rapid Detection of Flu A+B; BD Diagnostics, Sparks, MD, USA). The respiratory virus PCR multiplex panel was used to test for influenza A and B viruses, RSV, HMPV, HPIV, HRhV, and HAdV. Influenza-specific reverse transcription PCR was used to detect the influenza A (H1N1) during the 2009 H1N1 pandemic.

Definitions

URD was defined as the detection of a CRV in upper respiratory secretions, such as nasal or throat swabs, in association with respiratory symptoms, including cough, rhinorrhea, and sore throat, and in the absence of new infiltrates on chest imaging.[9,10] A LRD was defined as an acute respiratory illness with dyspnea, hypoxia, or pulmonary infiltrates occurring in association with the detection of a CRV in any respiratory secretions.[10] Assessment of the radiographic findings, including chest radiography and computed tomography scans, was based on the formal reading by a radiology specialist. Hospital-acquired infection was defined as symptom onset 3 or more days after hospital admission.[9] The presence of co-pathogens was defined as the isolation of pathogenic bacterial species, fungal species, or other opportunistic viruses, such as cytomegalovirus (CMV), from the respiratory specimen obtained within a month of detection of a CRV, in conjunction with consistent symptoms, and as confirmed by infectious disease specialists.[5] Proven or probable invasive fungal disease was defined according to the criteria of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group in 2008.[11] A mixed CRV infection was defined by the isolation of more than two CRVs during the same episode. Mortality due to LRDs caused by CRVs was defined as death resulting from respiratory failure, with no period of complete recovery between the onset of illness and death within 30 days, and without a documented co-pathogen.[12] Overall mortality was defined as death from any cause within 30 days following diagnosis of CRV-LRD. An absolute lymphocyte count (ALC) of <200 cells/mm^3 blood within the 2 weeks preceding a CRV infection diagnosis was defined as lymphopenia, and an absolute neutrophil count (ANC) of <500 cells/mm^3 blood within the 2 weeks prior to a CRV infection was defined as neutropenia.[6] The dosage of corticosteroid use was classified into three groups according to the highest daily dose taken by the patient during the 2 weeks preceding a CRV infection: high-dose corticosteroid use was defined as ≥1 mg/kg/day of prednisone and its equivalent dose of corticosteroids: low-dose use was defined as ≤1 mg/kg/day of prednisone; and the third group received topical corticosteroids.[13] The grade of immunodeficiency was classified into three groups, including severe, moderate, and mild immunodeficiency.[14] Severe immunodeficiency (SID) was defined as the presence of two or more of the following: allogeneic SCT (alloSCT) within 6 months, or autologous SCT (autoSCT) within 3 months, preceding the diagnosis of a CRV infection; acute GVHD (grade ≥2); ALC <200 cells/mm^3 or ANC <500 cells/mm^3 within 2 weeks, before the diagnosis; and a pre-engraftment period or administration of immunosuppressive therapy ≤2 weeks prior to the diagnosis. Moderate immunodeficiency (MID) was defined as the presence of only one criteria of SID or two or more of the following criteria: an alloSCT within 1 year (≥6 months) or an autoSCT within 6 months (≥3 months), prior to the diagnosis of a CRV infection; ALC between 200 and 500 cells/mm^3, or ANC between 500 and 1000 cells/mm^3, within 2 weeks before the diagnosis; and administration of immunosuppressive drugs within 1 month prior to the diagnosis. Patients who met

only one criterion of MID were regarded as having a mild immunodeficiency state.

Statistics

All analyses were performed for the first episode of CRV infection after SCT. Categorical variables are described as number (percentage). Continuous variables are expressed as medians (interquartile range) or mean±standard deviation. Categorical variables were compared using chi-square or Fisher's exact tests, and continuous variables were compared using t-tests or Wilcoxon rank-sum tests. Using Cox proportional hazards regression models, all variables with a $p<0.05$ upon univariate analysis were included in a multivariate logistic regression analysis to determine the significance of the risk factors for mortality associated with CRV-LRDs. All p values were two-tailed, and statistical significance was set at $p<0.05$. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Table 1. Baseline Characteristics of Hematopoietic Stem Cell Transplantation Recipients with Lower Respiratory Tract Diseases by Common Respiratory Viruses

Characteristics	Number of patients
Age (yrs)	44 (34–56)
Male	43 (64.2)
Underlying malignancy	
Acute myelogenous leukemia	25 (37.3)
Acute lymphoblastic leukemia	10 (14.9)
Multiple myeloma	13 (19.4)
Myelodysplastic syndrome	9 (13.4)
Non-hodgkin lymphoma	4 (6.0)
Others*	6 (8.9)
Transplantation type	
Autologous	17 (25.4)
Allogeneic	50 (74.6)
Matched, related	24 (35.8)
Mismatched or unrelated	21 (31.3)
Familial mismatched	5 (7.5)
Stem cell source	
Peripheral blood	46 (68.7)
Bone marrow	21 (31.3)
Conditioning regimen	
Myeloablative	26 (52.0)
Non-myeloablative	24 (48.0)
Presence of GVHD	26 (38.8)
Acute	9 (34.6)
Grade 1–2	7
Grade 3–4	2
Chronic	17 (65.4)
Limited	4
Extensive	13

GVHD, graft-versus-host disease.
Data are presented as n, n (%), or median (interquartile range).
*Others include chronic myelogenous leukemia (1), chronic lymphocytic leukemia (1), aplastic anemia (2), and mixed phenotype acute leukemia (2).

RESULTS

Characteristics of patients with CRV-LRDs

A total of 1038 patients received SCTs (273 autologous and 765 allogeneic) between January 1, 2007 and August 31, 2011. Over a 5-year period between 2007 and 2012, 71 CRV-LRDs were identified in 67 (6.5%) patients, and coinfection with more than two CRVs was observed in 4 (5.9%) patients. Influenza A virus and RSV coinfection was observed in two patients. HPIV and HRhV coinfection was observed in one patient, and HPIV and RSV coinfection was also observed in one patient. The baseline characteristics of the 67 SCT recipients with CRV-LRDs are shown in Table 1. During the winter, RSV and influenza A virus were the predominant CRVs, while the proportion of HPIV infection increased through spring and summer (Fig. 1). Analysis for cumulative incidences of first CRV-LRD episodes demonstrated that the most common causative pathogen of CRV-LRDs at both 100 days [cumulative incidence estimate, 23.5%; 95% confidence interval (CI), 3.3–43.7] and at 1 year after SCT (cumulative incidence estimate, 69.2%; 95% CI, 45.9–92.5) was HPIV. The cumulative incidence estimate of RSV was 6.9% (95% CI, 0.0–16.1), and only two patients presented with LRDs caused by influenza A virus and HRhV (one patient each) before 100 days following SCT (Fig. 2A). The cumulative incidence es-

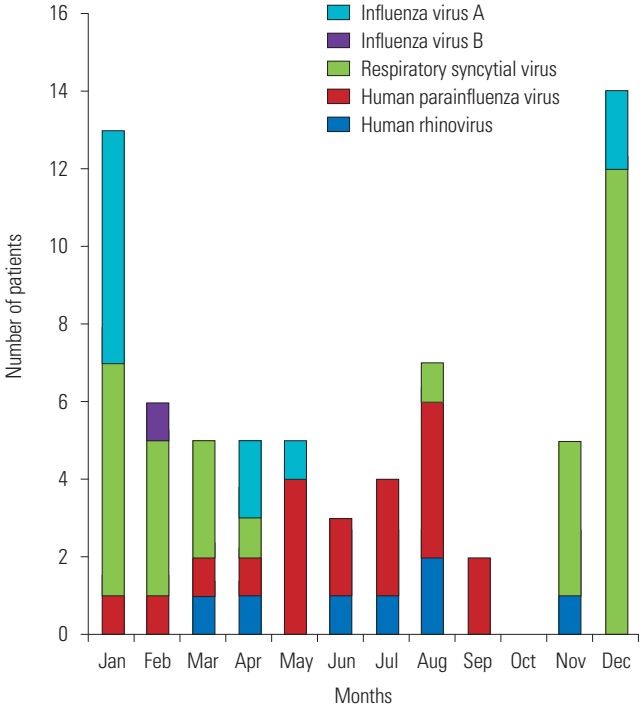

Fig. 1. Distribution of lower respiratory tract diseases caused by common respiratory viruses in hematopoietic stem cell transplantation recipients according to the month of the year.

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timates of LRDs caused by influenza virus, RSV, HPIV, and HRhV at 1 year after SCT were 42.9% (95% CI, 17.0–68.8), 21.6% (95% CI, 6.3–36.9), 69.2% (95% CI, 45.9–92.5), and 28.6% (95% CI, 0.0–62.1), respectively (Fig. 2B).

Clinical presentations and outcomes of CRV-LRDs

The characteristics of the LRDs caused by the various CRVs are described in Table 2. The most common type and extent of radiographic infiltration of influenza-caused LRDs were alveolar pattern (64.3%) and bilateral lung field (85.7%), respectively. Seven (50%) of 14 patients with influenza-LRDs received antiviral therapy, and all received it within 48 hours following influenza-LRD diagnosis. However, early antiviral therapy within 48 hours after symptom onset was performed for only 3 (21.4%) patients. One patient received combination therapy with peramivir (600 mg/day for 8 days) and oseltamivir (300 mg/day for 15 days). Five (35.7%) patients experienced mechanical ventilation, and the 30-day overall mortality rate of these patients was 35.7% (5/14). Two patients were diagnosed with the influenza A (H1N1) pdm09 virus, of which one died

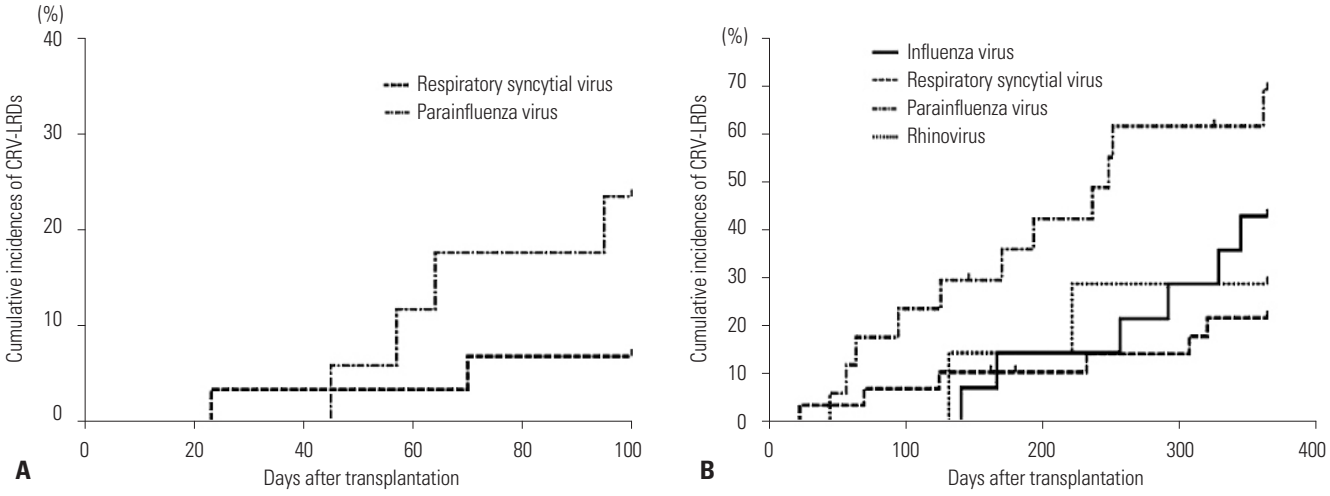

Fig. 2. Cumulative incidences of the first episodes of lower respiratory tract diseases caused by common respiratory viruses at 100 days (A) and 1 year (B) after hematopoietic stem cell transplantation. CRV, common respiratory virus; LRDs, lower respiratory tract diseases.

Table 2. Clinical Presentations and Outcomes of LRDs Caused by CRVs

	Influenza (n=14)	RSV A/B (n=31)	HPIV (n=19)	HRhV (n=7)	Total (n=71)
Hospital-acquired	5 (35.7)	13 (41.9)	14 (73.7)	4 (57.1)	36 (50.7)
Type of radiographic infiltrate					
Interstitial	5 (35.7)	12 (38.7)	8 (42.1)	4 (57.1)	29 (40.8)
Alveolar	9 (64.3)	18 (58.1)	11 (57.9)	3 (42.9)	41 (57.7)
Bronchitis	-	1 (3.2)	-	-	1 (1.4)
Extent of radiographic infiltrate					
Bilateral	12 (85.7)	21 (67.8)	17 (89.4)	6 (85.7)	56 (78.9)
Unilateral	-	1 (3.2)	1 (5.3)	1 (14.3)	3 (4.2)
Unilobar	2 (15.4)	9 (29.0)	1 (5.3)	-	12 (16.9)
Presence of co-pathogen	7 (50)	10 (32.3)	10 (52.6)	6 (85.7)	33 (46.5)
Bacteria	5	7	7	4	23
Molds	2	2	3	1	8
Viral other than CRV	-	1	-	1	2
Antiviral therapy	7 (50)	3 (9.7)	7 (36.8)	-	17 (23.9)
Antiviral therapy within 48 hrs after symptom onset	3 (21.4)	2 (6.5)	1 (5.3)	-	6 (8.5)
Hospitalization	12 (85.7)	26 (83.9)	17 (89.5)	6 (85.7)	61 (85.9)
Mechanical ventilation	5 (35.7)	9 (29.0)	12 (63.2)	4 (57.1)	30 (42.3)
Overall mortality at 30 days	5 (35.7)	8 (25.8)	6 (31.6)	3 (42.9)	22 (30.9)
Mortality due to CRV-LRDs within 30 days	2 (14.3)	7 (22.5)	5 (26.3)	1 (14.3)	15 (21.1)
Days from CRV-LRD to death	9.5 (3–30)	13 (6–24)	21 (16–34)	10 (NA)	16 (7–28)

CRV, common respiratory virus; LRD, lower respiratory tract disease; RSV, respiratory syncytial virus; HPIV, human parainfluenza virus; HRhV, human rhinovirus; NA, not available.
Data are presented as n (%) or median (interquartile range).

due to respiratory failure on day 28 following the diagnosis. Of the 31 patients with RSV-LRDs, 41.9% (13/31) were hospital-acquired and 9.7% (3/31) received antiviral therapy. The 30-day overall mortality rate was 25.8% (8/31) for these patients. Two patients with RSV-LRDs were treated with oral ribavirin, one with aerosolized ribavirin, and all received intravenous immunoglobulin (IVIG; 1–1.5 g/kg for 1–2 days). The patient who received aerosolized ribavirin and IVIG survived, whereas the two patients treated with oral ribavirin died. Seven (36.8%) of the 19 patients with HPIV-LRDs received oral ribavirin (800 mg/day for 11–26 days). The 30-day overall mortality rate of patients with HPIV-LRDs was 31.6% (6/19). Four (57.1%) of seven patients with HRhV-LRDs required mechanical ventilation, and the 30-day mortality rate for these patients was 14.3% (1/7). Co-pathogens isolated from respiratory specimens were detected in 33.8% (23/67) of patients with CRV-LRDs. The most common bacterial co-pathogen was *Acinetobacter baumannii* (n=7; 10.4%), followed by *Pseudomonas aeruginosa* (n=5; 7.4%) and *Streptococcus pneumoniae* (n=4; 5.9%). *Aspergillus* species were detected in 6 patients and CMV-PCR of the BAL fluid was positive for two patients. Only 2 patients died without pneumonia being the cause of death, one due to septic shock as a result of infectious colitis and one due to diffuse alveolar hemorrhage.

Risk factors for 30 day-mortality in SCT recipients with CRV-LRDs

The overall mortality at day 30 after the diagnosis of a CRV-LRD was 32.8% (22/67). In the univariate analysis, high-dose steroid usage (p=0.025), SID (p=0.033), and lymphopenia (p=0.006) were significantly associated with mortality within 30 days following a CRV-LRD diagnosis (Table 3). Multivariate logistic

Table 3. Comparison of Baseline Characteristics between Survivors and the Deceased within 30 days among 67 SCT recipients with CRV-LRDs

Characteristics	Survived >30 days after CRV-LRD (n=45)	Death ≤30 days after CRV LRD (n=22)	Univariate analysis (p value)
Age (yrs)*	43 (13)	44 (13)	0.905
Male	28 (62.2)	15 (68.2)	0.633
BMI*	22.2 (3.55)	22.9 (3.96)	0.520
Obesity (BMI>25)	7 (15.6)	6 (27.3)	0.260
Donor type			0.728
Autologous	12 (26.7)	5 (22.7)	
Allogeneic	33 (73.3)	17 (77.3)	
Conditioning regimen			0.489
Reduced intensity conditioning	17 (51.5)	7 (41.2)	
Myeloablative	16 (48.5)	10 (58.8)	
Stem cell source			0.536
Peripheral blood	32 (71.1)	14 (63.6)	
Bone marrow	13 (28.9)	8 (36.4)	
Presence of GVHD	16 (35.6)	10 (45.5)	0.436
Acute GVHD	5 (11.1)	4 (18.2)	0.425
Chronic GVHD	11 (24.4)	6 (27.3)	0.803
Use of steroids			0.025
No use, topical or low dose	35 (77.8)	11 (50)	
High dose	10 (22.2)	11 (50.0)	
Use of immunosuppressant	25 (55.6)	13 (59.1)	0.784
Grade of immunodeficiency			0.033
Meets no criteria or mild	13 (28.9)	3 (13.6)	
Moderate	17 (37.8)	4 (18.2)	
Severe	15 (33.3)	15 (68.2)	
Days from SCT to CRV-LRD			0.722
≤30 days	4 (8.9)	2 (9.1)	
30–100 days	5 (11.1)	4 (18.2)	
>100 days	36 (80.0)	16 (72.7)	
Days from SCT to CRV-LRD†	320 (409)	204 (276)	0.128
Lymphopenia (ALC<0.2×10^9/L)	6 (13.3)	10 (45.5)	0.006

CRV, common respiratory virus; LRD, lower respiratory tract disease; BMI, body mass index; GVHD, graft-versus-host disease; SCT, stem cell transplantation; ALC, absolute lymphocyte count.
*Data are presented as n (%), mean (SD), †Median (interquartile range).

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regression analysis revealed that the use of high-dose steroids [odds ratio (OR), 4.05; 95% CI, 1.12–14.61; p=0.033] and lymphopenia (OR, 6.57; 95% CI, 1.80–24.03; p=0.004) were independent risk factors for mortality within 30 days of CRV-LRD detection (Table 4).

DISCUSSION

There has been almost no data on respiratory virus infection among SCT recipients in Korea. This study aimed to retrospectively collect and analyze data regarding the epidemiology and risk factors of LRDs caused by CRVs in SCT recipients from the largest SCT center in Korea.

The incidences of influenza-associated LRD among SCT recipients reported in other studies ranged from 0.4–4.1%, and the mortality rates were 14.7–28%.[5,6,10,15] In previous studies, the proportions of progression to pneumonia among influenza virus-infected SCT recipients were reported as 29–43%.[15,16] The 30-day mortality rate of influenza-LRD at our center was 14.3%, which is consistent with the previous reports.

RSV infections have been reported to occur in 1.2–9.6% of adult SCT recipients.[5,17,18] The incidences and mortality rates of RSV-LRDs among SCT recipients were reported as 2.9–5.1% and 16.7–50%, respectively.[5,6,14,17] These findings are consistent with the incidence (2.7%) and mortality rate (22.5%) of RSV-LRD observed at our center, in spite of the low rate of ribavirin treatment (9.7%). Known risk factors of RSV-associated mortality in SCT patients included pre-engraftment, lymphopenia, alloSCT <1 month previously, SID, and an older age (>65 years).[14,19] The highest incidence of RSV occurred between January and April, which is consistent with our result that the majority of RSV-LRDs were detected between December and March.[20]

Symptomatic HPIV infections have been reported to occur in 1.4–7.1% of adult SCT recipients in previous studies.[5,21,22] The reported frequency and mortality rates of HPIV-LRDs among SCT recipients were 0.05–8.1% and 11.8–46%, respectively.[5,6,9,10,22-24] The 30-day mortality rate of HPIV-LRD at our center, 26.3% (5/19), was similar to that of previous studies, despite the low rate of antiviral treatment (36.8%). Since HPIV showed the highest cumulative incidence of LRDs at 100 days (23.5%; 95% CI, 3.3–43.7) and 1 year (69.2%; 95% CI, 45.9–92.5) following SCT, the performance of a laboratory examination is important due to non-specific respiratory symptoms. Independent predictors of HPIV-associated death that have been reported in the literature include steroid usage, cancer status, Acute Physiology and Chronic Health Evaluation II score, LRD, infection immediately following SCT (<30 days), mismatched donor, the need for mechanical ventilation, and the presence of co-pathogens.[9,22,23] Similarly, high-dose steroid usage at the time of diagnosis was one of the independent predictors of death among SCT recipients with CRV-LRDs in the present study. Furthermore, the present study demonstrated that HPIV infections were most prevalent in the summer months, followed by spring, which had been reported previously.[9,22]

Previous studies reported that the incidence of HRhV-LRD among SCT recipients is rare (0–1.4%), and that HRhV-LRDs are associated with low mortality rates.[5,25] In the present study, the incidence of HRhV-LRD was 0.7% (7/1038 patients) and the associated 30-day mortality rate was 14.3% (1/7 patients). These results are consistent with the preceding studies that HRhV may cause severe infections in SCT recipients, with high rates of progression to LRD and mortality.[18,26,27] Ison, et al.[28] reported that all 6 SCT recipients with pneumonia in whom HRhV was detected in BAL had significant coinfections and suggested that HRhV might be a cause of frequent superinfections, possibly through lytic infection or an indirect immunosuppressive effect. Our study also indicated that 42.9% (3/7) of patients with HRhV-LRDs were positive for the presence of co-pathogens.

HAdV has been shown to infect up to 3% of SCT recipients, and the subsequent mortality rate can be high (15–28%).[29] HMPV-LRDs have been reported to occur in 0.7–1.2% of SCT recipients, of which 0–40% progressed to death.[5,30] However, no cases of HAdV-LRDs or HMPV-LRDs were observed in our patient cohort.

CRV infection may contribute to sustained inflammation or activation of an inflammatory process that leads to irreversible airway damage, and can cause late airflow obstruction in SCT recipients.[31] Furthermore, CRV infections frequently coexist

Table 4. Univariate and Multivariate Logistic Regression Analysis for Mortality within 30 Days Following Lower Respiratory Tract Diseases Caused by Common Respiratory Virus Diagnosis among Hematopoietic Stem Cell Transplantation Recipients

Variables	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Use of high-dose steroid	3.50 (1.17–10.43)	0.025	4.05 (1.12–14.61)	0.033
Grade of immunodeficiency				0.831
Meets no criteria or mild	1	0.033	1	
Moderate	1.02 (0.19–5.37)		0.77 (0.13–4.40)	
Severe	4.33 (1.02–18.38)		1.28 (0.2–7.95)	
Lymphopenia* (ALC<200 cells/mm^3)	5.42 (1.63–18.01)	0.006	6.57 (1.80–24.03)	0.004

OR, odds ratio; CI, confidence interval; ALC, absolute lymphocyte count.
*ALC of blood encountered during the 2 weeks before common respiratory virus infection diagnosis.

with bacterial or fungal pathogens, contributing to the development of pneumonia. It may be the result of epithelial damage, impaired ciliary function, an altered immune response, or upregulation of bacterial receptors on the CRV-infected respiratory tract.[16,32] In addition, there have been several reports that SCT recipients have shown a lower immune response to the influenza vaccine compared with that observed for the general population.[33,34] Severely immunocompromised patients, such as SCT recipients, have been reported to show prolonged influenza shedding, resulting in the development of antiviral resistance during prolonged antiviral therapy.

In the present study, high-dose steroid usage and lymphopenia were shown to be risk factors for mortality in SCT recipients with CRV-LRDs. Lymphopenia was previously reported as a risk factor for mortality among SCT patients with LRDs caused by influenza or RSV.[6,13,19] Additionally, high-dose steroid usage during the 2 weeks preceding a CRV-LRD diagnosis was reported as an independent predictor of mortality among SCT recipients with HPIV-LRDs.[9,23] It is likely that these two risk factors are associated with a decreased T-cell-mediated immune response.[22] Furthermore, high-dose corticosteroid use is known to be associated with a trend toward delayed viral clearance.[35] Conversely, a few previous studies reported that the use of corticosteroids exerted protective effects against the progression to pneumonia and requirement for mechanical ventilation among SCT recipients with influenza-LRDs, which was hypothesized to occur due to a salutary immunomodulatory effect.[13,15]

There are several limitations of the present study. As this was a retrospective study, there were no standardized guidelines for the screening and treatment of CRV infections. However, to overcome this limitation, only CRV-LRD cases were included. Due to the small number of cases, it was not possible to analyze the risk factors for mortality for individual CRV-LRDs. Another limitation was that it was difficult to determine whether the fatal outcome was solely attributable to the CRV or due to a combination of the CRV and co-pathogens. However, precise discrimination of the pathogen would likely have been meaningless, since damage to the respiratory epithelium as a result of a CRV infection may have been the key factor that facilitated the occurrence of superinfections.[9] Recent studies showed that viral nucleic acid was detected in the bloodstream more frequently among SCT recipients with LRDs caused by influenza, RSV, HAdV, and HMPV, and that this was associated with increased mortality rates.[36-38] Therefore, viral nucleic acid detection in the bloodstream of SCT recipients with CRV-LRDs could be used to predict disease severity, poor outcome, and the need for intensified antiviral treatment in the future.

Our study demonstrated that CRV-LRDs have a significant morbidity and mortality among SCT recipients; thus, the implement of an active diagnostic approach for CRV infection is required for SCT recipients with respiratory symptoms. For SCT recipients with LRDs caused by influenza, RSV, or HPIV infections, those receiving high-dose steroid treatment or those with lymphopenia, early antiviral treatment should be considered; especially considering the fact that no vaccine is yet available for RSV and HPIV. Furthermore, infection control measures, including hand hygiene and respiratory droplet isolation, which reduce the occurrence of new infections and transmission, are important for CRVs without a specific antiviral treatment option, such as HRhV and HMPV. Finally, in order to prevent LRDs caused by influenza, which is the only CRV with an available vaccine, the annual seasonal influenza vaccination is recommended for all SCT recipients.

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