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Pulmonary Impairment after Respiratory Viral Infections Is Associated with High Mortality in Allogeneic Hematopoietic Cell Transplant Recipients

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A B S T R A C T

Pulmonary impairment predicts increased mortality in many settings, and respiratory viral infection (RVI) causes considerable morbidity and mortality in allogeneic hematopoietic cell transplant recipients (allo-HCT). We hypothesized that pulmonary impairment after RVI, defined as a decline of forced expiratory volume in 1 second values by ≥10%, may identify allo-HCT recipients at high risk for mortality. We studied all allo-HCT recipients at our institution who had RVI with respiratory syncytial virus, parainfluenza virus, or influenza from 2004 to 2013 and had pre-RVI and post-RVI pulmonary function tests. We used competing risk regression models to identify risk factors for 2-year nonrelapse mortality (NRM) as the primary outcome after RVI and relapse-related mortality as a competing risk. From 223 eligible patients, pulmonary impairment after RVI was associated with over a 3-fold increase in 2-year NRM (pulmonary impairment, 25.3%; no impairment, 7.4%; univariate subhazard ratio [SHR], 3.9; 95% confidence interval [CI], 1.9 to 8.1; $P < .001$). After adjusting for age and systemic steroid use, pulmonary impairment after RVI was still associated with increased 2-year NRM (SHR, 3.3 [95% CI, 1.6 to 6.9]; $P = .002$). After adjustment for race and graft-versus-host disease (GVHD) prophylaxis, chronic GVHD at the time of RVI (odds ratio [OR], 2.8 [95% CI, 1.4 to 5.4]; $p = .003$) and lymphopenia (OR, 2.2 [95% CI, 1.1 to 4.2]; $P = .02$) were associated with increased odds of pulmonary impairment, whereas use of nonmyeloablative conditioning was associated with reduced odds of pulmonary impairment (OR, .4 [95% CI, .2 to .8]; $P = .006$). In allo-HCT recipients with RVIs, pulmonary impairment after RVI is associated with high NRM at 2 years.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is an important curative option for many refractory and high-risk malignancies [1]. Respiratory viral infections (RVIs) are increasingly recognized as important causes of morbidity and mortality in the general population [2] and are particularly common after HCT [3,4]. Depending on the viral species, more than 30% of RVIs in HCT recipients progress to lower respiratory tract infections (LRIs) [3], resulting in high mortality [5-9]. About 30% of allogeneic HCT (allo-HCT) recipients develop LRI after respiratory syncytial virus (RSV) infection, and the overall mortality rate after RSV infection is about 16% [10]. Similarly, around half of all HCT recipients with parainfluenza virus (PIV) develop LRI [11], with an overall mortality rate of 7% to 10%, and about 30% of all HCT recipients with H_1N_1 influenza virus (FLU) develop LRI [12], with an overall mortality rate of about 6%. Identification of HCT recipients at high risk for death after RVI is of paramount importance.

Impairments in pulmonary function have long been linked to decreased survival in the general population [13]. Independent of tobacco use, declines in forced spirometric measurements are associated with increased all-cause [14-16] and cardiovascular mortality [17,18]. Pulmonary impairment is a common complication after RVIs in the general population [19,20]. In allo-HCT recipients RVIs have been associated with bronchiolitis obliterans

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syndrome (BOS), a form of graft-versus-host disease (GVHD) of the lung [21,22]. BOS occurs in about 5% of HCT recipients [23], and mortality primarily occurs in patients with the most severe impairments in lung function [24-27]. Outside of BOS, the association of pulmonary impairment with mortality has not been well studied in allo-HCT recipients. A previous single-center study of 442 allo-HCT recipients found that declines in forced expiratory volume in 1 second (FEV_1) of at least 10% were not associated with higher mortality [28]. No studies have examined the impact of pulmonary impairment on survival in allo-HCT recipients who develop RVIs.

FEV_1 is a highly reproducible measurement that predicts mortality in many populations [29,30]. Because allo-HCT recipients who develop RVIs are at a high risk for mortality, we sought to determine whether declines in FEV_1 of at least 10% after RVI could predict nonrelapse mortality (NRM) in allo-HCT recipients. To that end, we conducted a retrospective review of all allo-HCT recipients at our institution who had RSV, PIV, or FLU infection. We hypothesized that allo-HCT recipients who developed pulmonary impairment after RVI would have higher NRM than those who did not, similar to the findings in other populations.

METHODS

Subjects

Clinical data on all allo-HCT recipients with RSV, PIV, or FLU infection at The University of Texas MD Anderson Cancer Center obtained at the time of RVI from August 2004 to July 2013 were collected from prospectively maintained institutional infection control and HCT databases. Patients who had multiple RVIs during the study period were excluded to better understand the impact of a single RVI on mortality. Those who did not complete post-RVI pulmonary function tests (PFTs) were also excluded because their declines in FEV_1 could not be calculated. In addition, to understand the impact of new pulmonary impairment in allo-HCT recipients, we excluded allo-HCT recipients with BOS before RVI. The MD Anderson Institutional Review Board approved the study (PA12-0407) with a waiver of informed consent.

Definitions for RVIs

Patients were considered to have RVIs if they had acute signs and symptoms of respiratory infection (eg, fever, rhinorrhea, cough, nasal congestion) and a nasal wash or bronchoalveolar lavage specimen positive for RSV, PIV, or FLU in viral culture and/or a direct immunofluorescent assay as per our institutional practices during the study period. Upper respiratory tract infection was defined as viral detection in nasal specimens and no pulmonary infiltrates on thoracic images. LRI was defined as new or changing pulmonary infiltrates on thoracic images and viral detection in nasal specimens and/or bronchoalveolar lavage fluid. Patients who had resolving infiltrates or volume overload as assessed via clinical chart review were not considered to have LRIs. Respiratory co-infections were defined as the detection of any viral or nonviral pulmonary pathogen other than RSV, PIV, or FLU at the time of RVI. Antiviral therapy was defined as any therapy specifically for RVI (eg, ribavirin for RSV or oseltamivir for FLU). We considered absolute neutrophil counts $< 500 \times 10^6$ cells/L to indicate neutropenia and absolute lymphocyte counts (ALCs) $< 500 \times 10^6$ cells/L to indicate lymphopenia.

Pulmonary Function Testing

PFT results for all study patients were collected from our institutional PFT database. Patients who did not undergo postinfection PFTs within 1 year after RVI were excluded. The PFT immediately preceding RVI was considered the baseline PFT, and the PFT with the lowest FEV_1 performed 14 to 365 days after RVI was considered the post-RVI PFT. We chose the earlier cut-off point of 14 days to exclude patients with very early pulmonary impairment after RVI and chose the later cut-off point of 365 days to allow for sufficient time for patients to undergo post-RVI PFTs, while limiting the window of risk after RVI to 1 year. Declines in FEV_1 of at least 10% from pre-RVI values were considered to represent significant pulmonary impairment. All 4 National Institutes of Health criteria for BOS were required for a diagnosis of National Institutes of Health-BOS: FEV_1/forced vital capacity ratio $< .7$ or below the fifth percentile of predicted values; $FEV_1 < 75\%$ of predicted values, with a $>10\%$ decline over a period shorter than 2 years; absence of infection in the respiratory tract documented in investigations directed by clinical symptoms; and evidence of air trapping, small airway thickening, or bronchiectasis on computed tomography images, residual volume/total lung capacity ratios elevated outside the 90% confidence interval (CI) for predicted values, residual volume $> 120\%$ of predicted values, or evidence of GVHD in a nonlung organ [31].

Statistical Analysis

Descriptive statistics were calculated for demographic, clinical, and outcome data. Categorical variables were compared using chi-square or Fisher exact tests, and continuous variables were compared using Student's *t*-tests. Unadjusted odds ratios (ORs) and 95% CIs with their *P* values were calculated for each independent variable and post-RVI FEV_1 decline (10%) using logistic regression. Next, a final multivariable model was constructed using forward selection with Bayesian information criteria to identify risk factors associated with post-RVI FEV_1 decline. The Hosmer-Lemeshow goodness-of-fit statistic was used to check the fit of the final model. Fine-Gray models [32] were constructed for each risk factor for the primary outcome of 2-year NRM, and relapse-related mortality (RRM), as defined by the Center for International Blood and Marrow Transplant Research guidelines [33], as a competing risk.

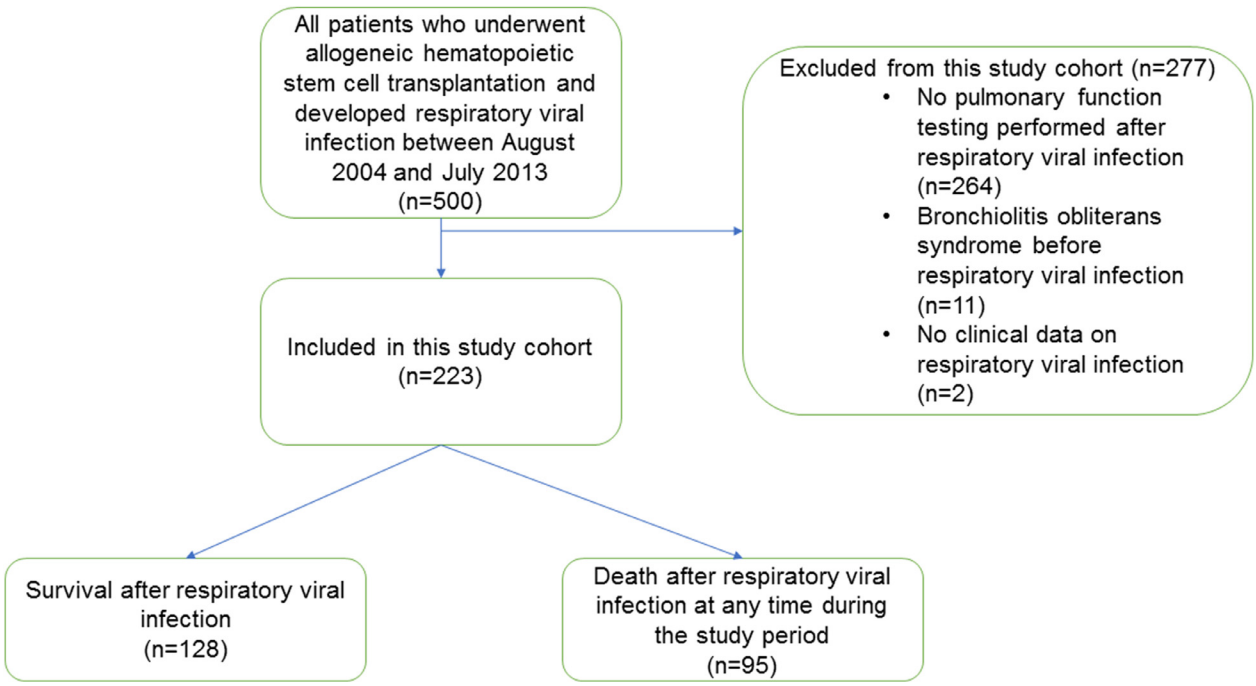

Figure 1. Enrollment flow chart for the study cohort.

Allo-HCT recipients must have died without evidence of relapsed malignancy within 2 years of RVI to fulfill the primary outcome of 2-year NRM. We chose the 2-year landmark to allow for allo-HCT recipients with pulmonary impairment late in the 1-year period after initial RVI to have at least 1 year of observation after the time of pulmonary impairment. Subhazard ratios (SHRs) and 95% CIs with their *P* values were calculated for each independent variable and 2-year NRM. All covariates found to be significant in these univariable models ($P \leq .1$) were included in the multivariable model. Variables were retained in the final model only if they were significant at $P = .05$ or if they induced a ≥15% change in the OR of another significant variable of primary interest, indicating confounding. Similar analyses were repeated in separate models with 1-year NRM and any NRM as outcomes of interest with 1-year RRM and any RRM as the competing events, respectively. Cumulative incidence failure curves were used to compare the probability of 2-year NRM of patients in whom pulmonary impairment developed (either 10% post-RVI FEV_1 decline or BOS) with that in patients who did not have this impairment, adjusted for age and use of corticosteroids.

All statistical analyses were performed using the R programming language (version 3.3; R Foundation for Statistical Computing, Vienna, Austria) and the Intercooled STATA software program (version 13.1; StataCorp, College Station, TX). All tests were 2-sided, with a significance and $P = .05$ considered significant.

RESULTS

Characteristics of the Study Cohort

Figure 1 shows the flow chart for our cohort of patients in whom RVIs developed during the study period, after exclusion of those who did not meet our inclusion criteria. The primary reason for exclusion was absence of PFT data after RVI. We identified 223 patients who met our study criteria. In the study cohort the median time from the PFT immediately preceding RVI to RVI was 73 days (range, 1 to 1591), whereas the median time from RVI to the first PFT obtained after RVI was 65 days (range, 16 to 359). Of note, excluded patients were more likely to have RVIs after day 100 post-HCT (63% versus 51%, $P = .03$) and had higher all-cause mortality (53% versus 32%, $P < .001$) and NRM (31% versus 13%, $P < .001$) rates at 2 years after RVI than study patients. Table 1 depicts the characteristics of the study cohort.

Table 1
Characteristics of the Study Cohort (N = 223)

Characteristic	Value
Median age, yr (range)	52 (19–77)
Gender	
Male	127 (57)
Female	96 (43)
Underlying malignancy	
Acute leukemia	125 (56)
Chronic leukemia	34 (15)
Lymphoma/myeloma	61 (27)
Other	3 (1)
Days from HCT to RVI	
0-30	27 (12)
31-100	82 (37)
>100	114 (51)
HCT type	
Matched related donor	106 (48)
Matched unrelated donor	91 (41)
Mismatched	7 (3)
Haploidentical	6 (3)
Cord blood	13 (6)
Conditioning regimen	
Myeloablative	133 (60)
Nonmyeloablative	90 (40)
T cell depletion	
No	120 (54)
Yes	103 (46)
GVHD prophylaxis	
CNI/MTX	192 (86)
CNI/MMF	24 (11)
Other	7 (3)
History of acute GVHD before RVI	
No	114 (51)
Yes	109 (49)
History of chronic GVHD before RVI	
No	156 (70)
Yes	67 (30)
CMV seropositivity*	
Donor−/recipient−	25 (11)
Donor+/recipient+	94 (42)
Donor−/recipient+	86 (39)
Donor+/recipient−	17 (8)
RVI type	
RSV	68 (30)
FLU	40 (18)
PIV	115 (52)
All-cause mortality at 2 years post-RVI	
No	152 (68)
Yes	71 (32)
NRM at 2 years post-RVI	30 (13)
RRM at 2 years post-RVI	41 (18)

Values are n (%) unless otherwise defined. CNI indicates calcineurin inhibitor; MTX, methotrexate; MMF, mycophenolate mofetil; CMV, cytomegalovirus.
*CMV seropositivity data were unavailable for 1 patient in this study.

Predictors of Pulmonary Impairment after RVI

Within 1 year after RVI, 75 patients developed significant pulmonary impairment (34%). Of these 75 patients, 12 eventually developed BOS, of whom 11 developed BOS within 1 year of RVI. The median time to the diagnosis of BOS was 136 days after RVI (interquartile range, 22 to 708). Table 2 summarizes the bivariable and multivariable logistic regression models for the prediction of pulmonary impairment within 1 year after RVI. In the multivariable model, after adjustment for race and type of GVHD prophylaxis, chronic GVHD at the time of RVI (OR, 2.8 [95% CI, 1.4 to 5.4]; $P = .003$) and lymphopenia (OR, 2.2 [95% CI, 1.1 to 4.2]; $P = .02$) were associated with increased odds of pulmonary impairment, whereas use of nonmyeloablative conditioning was associated with reduced odds of pulmonary impairment (OR, .4 [95% CI, .2 to .8]; $P = .006$). We observed no significant differences in the odds of pulmonary impairment among patients who had RSV, PIV, or FLU infections (Table 2). Figure 2 shows a histogram of changes in FEV_1 from pre-RVI to post-RVI values in all patients and in those with RSV, PIV, or FLU infection. Figure 3 shows a histogram of time to pulmonary impairment among decliners who had RVI. There was no significant difference in time to the diagnosis of pulmonary impairment among patients with RSV, PIV, or FLU infection ($P = .35$).

Predictors of 2-Year NRM after RVI

During the study period, 71 patients (30%) had a fatal outcome by 2 years after RVI. Of these 71 patients, 40 developed RRM and 31 developed NRM. Table 3 shows unadjusted and adjusted competing risk models in which the primary outcome was 2-year NRM and the competing risk was 2-year RRM. In the multivariable competing risk model increased age (SHR, 1.4 per 10-year interval [95% CI, 1.0 to 1.8]; $P = .03$), systemic steroid use in the 30 days before RVI (SHR, 5.3 [95% CI, 2.0 to 13.7]; $P = .001$), and significant pulmonary impairment after RVI (SHR, 3.3 [95% CI, 1.6 to 6.9]; $P = .002$) remained significant predictors of death. The proportional hazards assumption was met, and there was no loss to follow up at 2 years.

Figure 4 shows cumulative incidence function curves for mortality among patients with and without significant pulmonary impairment. Survival was significantly lower among allo-HCT recipients with significant pulmonary impairment. Two-year NRM was 25.3% in patients with pulmonary impairment after RVI, as compared with 7.4% among those without impairment. Two-year NRM was similar among patients who developed pulmonary impairment within 90 days of RVI (33% 2-year NRM [10/

Table 2
Bivariable and Multivariable Risk Factors for Pulmonary Impairment after RVI

Characteristic	Nondecliners (n = 148)	Decliners (n = 75)	Unadjusted		Adjusted	
			OR (95% CI)	*P*	OR (95% CI)	*P*
Median age at time of RVI,* yr (range)	51 (19-72)	55 (19-77)	1.1 (.9-1.4)	.34		
Gender, n (%)						
Male	87 (59)	40 (53)	1.0			
Female	61 (41)	35 (47)	1.3 (.4-1.5)	.44		
Race,† n (%)						.36
White	112 (78)	61 (82)	1.0	.42	1.0	
Nonwhite	32 (22)	13 (18)	.8 (.4-1.5)		.7 (.3-1.5)	
Underlying malignancy, n (%)						
Acute Leukemia	78 (53)	47 (63)	1.0			
Chronic Leukemia	24 (16)	10 (13)	.7 (.3-1.6)	.38		
Lymphoma/myeloma	44 (30)	17 (23)	.6 (.3-1.3)	.19		
Other	2 (1)	1 (1)	.8 (.1-9.4)	.88		
Days between HCT and RVI						
≤100	73 (49)	36 (48)	1.0			
>100	75 (51)	39 (52)	1.1 (.6-1.8)	.85		
HCT type, n (%)						
Matched related donor	73 (49)	33 (44)	1.0			
Matched unrelated donor	58 (39)	33 (44)	1.3 (.7-2.3)	.45		
Mismatched	5 (3)	2 (3)	.9 (.2-4.8)	.89		
Haploidentical	6 (4)	0	—	—		
Cord blood	6 (4)	7 (9)	2.6 (.8-8.3)	.11		
Steroids 30 days before RVI, n (%)						
No	81 (55)	32 (43)	1.0			
Yes	67 (45)	43 (57)	1.4 (.6-2.9)	.09		
GVHD prophylaxis, n (%)						
CNI/MTX	127 (86)	65 (87)	1.0	.45	1.0	.10
CNI/MMF	14 (9)	10 (13)	1.4 (.6-3.3)		2.2 (.9-5.7)	
Other	7 (5)	0	—		—	
History of acute GVHD before RVI, n (%)						
No	79 (53)	35 (47)	1.0			
Yes	69 (47)	40 (53)	1.3 (.8-2.3)	.34		
History of chronic GVHD before RVI, n (%)						
No	112 (76)	44 (59)	1.0		1.0	
Yes	36 (24)	31 (41)	**2.2 (1.2-4.0)**	**.01**	**2.8 (1.4-5.4)**	**.003**
CMV seropositivity,‡ n (%)						
Donor−/recipient−	16 (11)	9 (12)	1.0			
Donor or Recipient+	131 (89)	66 (88)	.9 (.4-2.1)	.80		
RVI species, n (%)						
RSV	48 (32)	20 (27)	1.0			
FLU	26 (18)	14 (19)	1.3 (.6-3.0)	.55		
PIV	74 (50)	41 (55)	1.3 (.7-2.5)	.39		
Nonmyeloablative conditioning, n (%)						
No	80 (54)	43 (57)	1.0		1.0	
Yes	68 (46)	32 (43)	**.5 (.3-.9)**	**.02**	**.4 (.2-.8)**	**.006**
T cell depletion						
No	83 (56)	53 (71)	1.0			
Yes	65 (44)	22 (29)	1.3 (.7-2.3)	.34		
ALC at time of RVI						
$\geq 500 \times 10^6$ cells/L	99 (67)	42 (56)	1.0		1.0	
$< 500 \times 10^6$ cells/L	49 (33)	33 (44)	1.2 (.9-1.4)	.11	**2.2 (1.1-4.2)**	**.02**
ANC at time of RVI						
$\geq 500 \times 10^6$ cells/L	140 (95)	71 (95)	1.0			
$< 500 \times 10^6$ cells/L	8 (5)	4 (5)	1.0 (.7-1.5)	.98		
Site of infection at time of RVI						
Upper respiratory tract infection	121 (82)	50 (67)	1.0			
LRI	27 (18)	25 (33)	**2.2 (1.2-4.2)**	**.01**		
Co-infection at time of LRI						
No	127 (86)	57 (76)	1.0			
Yes	27 (14)	18 (24)	1.1 (.7-2.0)	.64		
Antiviral therapy at time of LRI						
No	60 (41)	28 (37)	1.0			
Yes	88 (59)	47 (63)	1.1 (.7-2.0)	.64		

ANC indicates absolute neutrophil count.
Statistically significant findings are highlighted in bold.
*Analyzed in increments of 10 years.
†Data for race were unavailable for 5 patients.
‡CMV seropositivity data was unavailable for 1 patient.

33]; SHR, 4.9 [95% CI, 2.1 to 11.5]; $P < .001$) and those who developed pulmonary impairment more than 90 days after RVI (21% 2-year NRM [9/42]; SHR, 3.2 [95% CI, 1.3 to 7.6]; $P = .01$). There was no difference in 2-year NRM in allo-HCT recipients with post-RVI pulmonary impairment who developed airflow obstruction as compared with those with post-RVI pulmonary

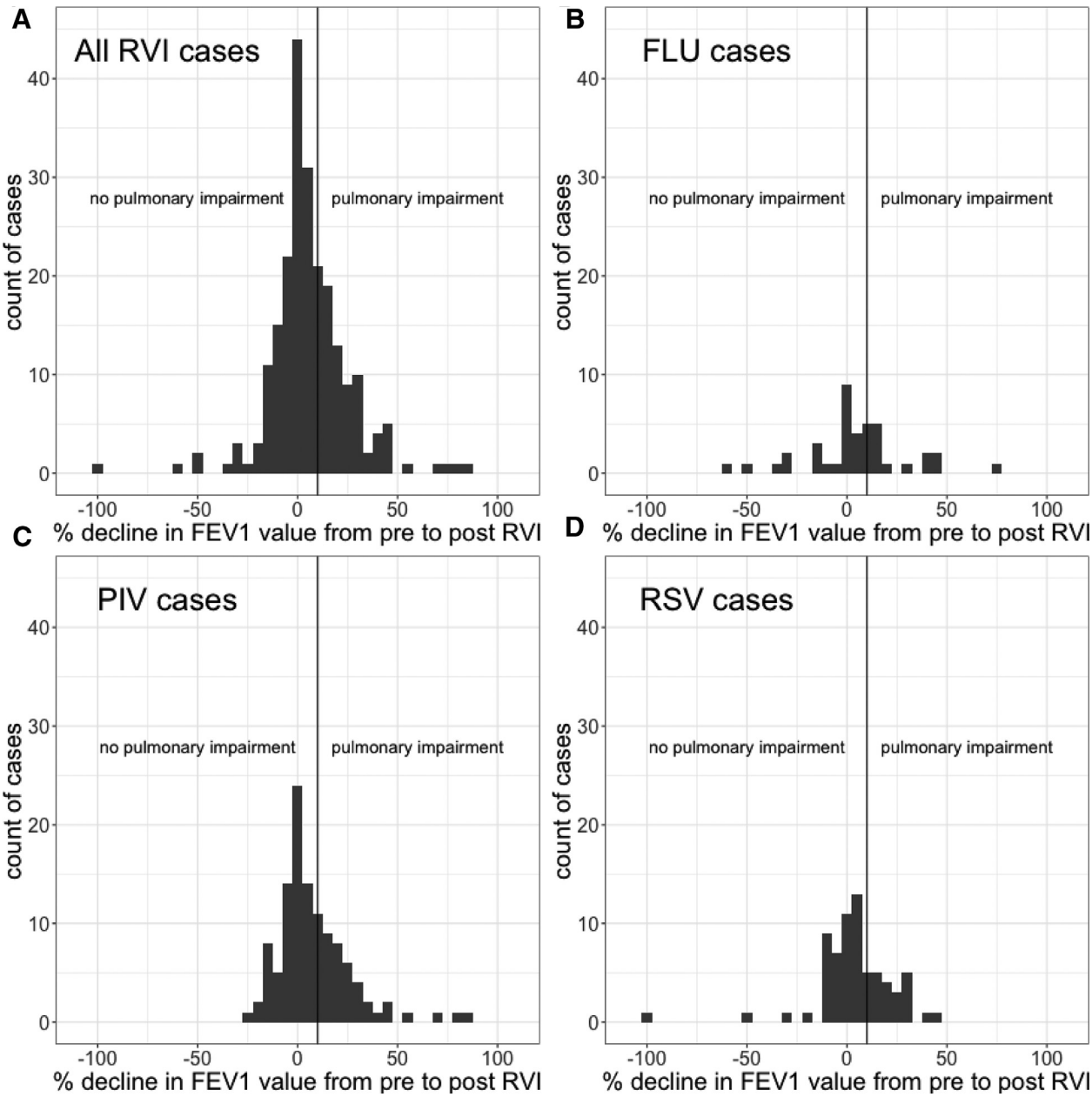

Figure 2. Histogram showing changes in FEV_1 from pre-RVI to post-RVI values in (A) the entire study cohort and in patients with (B) FLU infection, (C) PIV infection, and (D) RSV infection. The magnitude of FEV_1 decline did not differ significantly between viral species.

impairment but without airflow obstruction (obstruction: 2-year NRM 29% [5/17]; no obstruction: 2-year NRM 24% [14/58]; SHR, 1.2 [95% CI, .5 to 3.7]; $P = .68$).

DISCUSSION

In this study of allo-HCT recipients who had RSV, PIV, or FLU infections, we observed that pulmonary impairment, defined as at least 10% decline in FEV_1 from pre-RVI values, was an independent predictor of 2-year NRM after RVI. Myeloablative conditioning regimens during HCT and LRI at the time of RVI were predictive of pulmonary impairment after RVI. Among those with pulmonary impairment, NRM was high regardless of whether or not impairment was diagnosed within 90 days of RVI or was associated with airflow obstruction. Our findings suggest that screening for pulmonary impairment after RVI may identify allo-HCT recipients at high risk for NRM.

Although risk factors for post-HCT BOS have been well described [23,26,34-40], data on the risk of pulmonary impairment after RVI in allo-HCT recipients are lacking. RVIs are common in allo-HCT recipients, although incidence rates are likely to be underestimated by a lack of routine screening [4,41]. Short-term pulmonary impairment after RVI has been well described in the general population, although long-term data are lacking [19,20]. Impairments after certain RVIs, such as influenza, are associated with increases in airway resistance in normal individuals that may last for weeks [42-44]. In our study we found that 34% of allo-HCT recipients who developed RVI had a significant pulmonary impairment within 1 year of RVI, with about half of impairments occurring within 90 days of RVI.

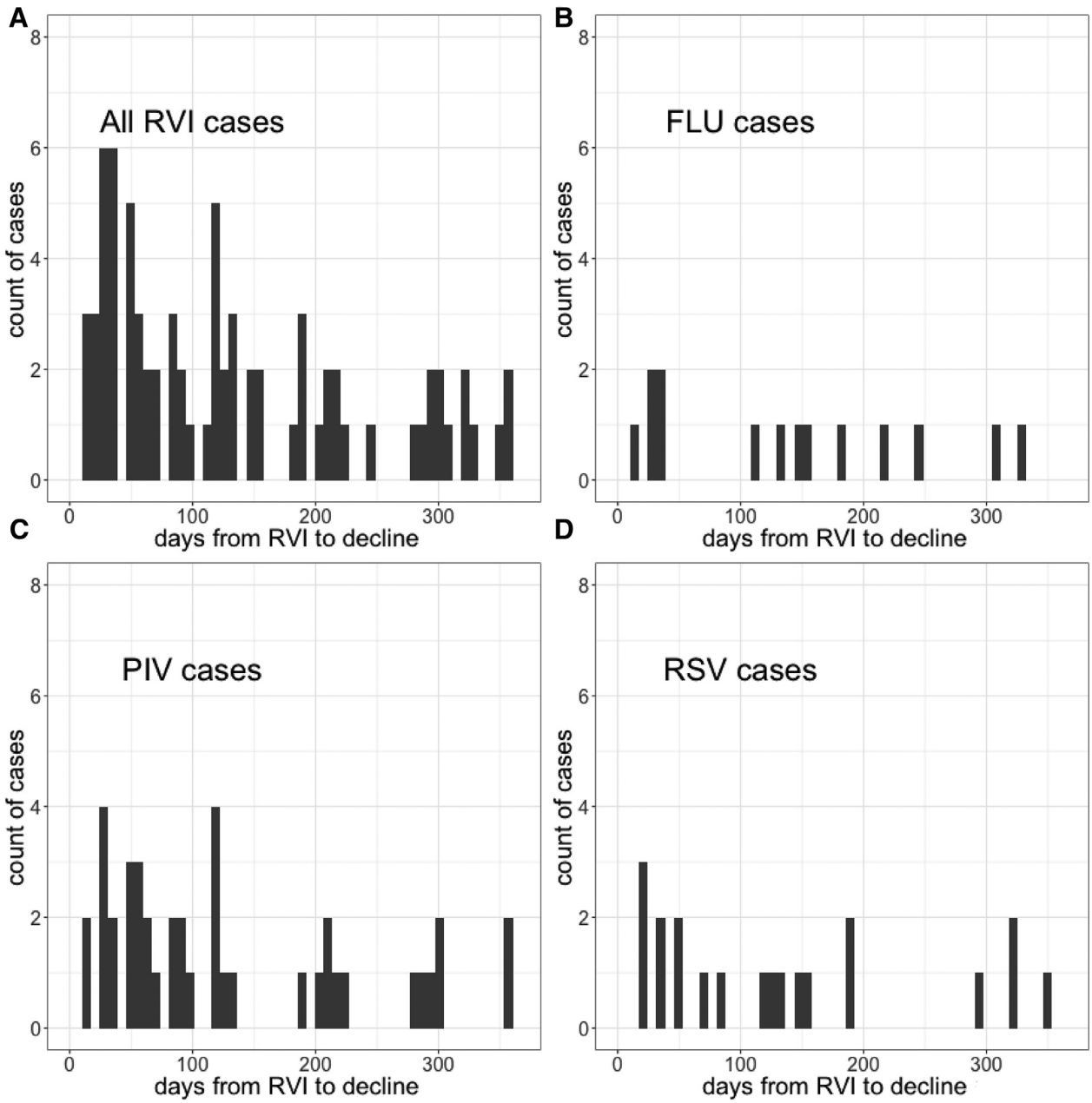

Figure 3. Histogram showing days to decline among patients with significant pulmonary impairment after RVI in (A) the entire study cohort and in patients with (B) FLU infection, (C) PIV infection, and (D) RSV infection. Each bin represents 1 week of time. There was no significant difference in time to decline after RVI between viral species.

Similar to the study by Erard et al. [21], which examined risk factors for BOS in allo-HCT recipients, in our univariate analyses we found that LRI at the time of RVI was a strong predictor of pulmonary impairment. However, in the multivariate model LRI was no longer predictive of pulmonary impairment. Instead, we observed that patients who received myeloablative conditioning regimens were at higher risk for pulmonary impairment after RVI than those who received nonmyeloablative regimens, similar to the known increase in the risk for BOS with myeloablative conditioning in allo-HCT recipients [45]**.** In allo-HCT recipients myeloablative conditioning and nonmyeloablative conditioning regimens are associated with similar rates of RVI, but progression to LRI and mortality is higher among those receiving myeloablative conditioning [46-48]. Additionally, we found that the presence of chronic GVHD before RVI predicted post-RVI pulmonary impairment. In allo-HCT recipients with chronic GVHD who develop RVI, it is possible that the requirement for systemic immunosuppression mediates much of the risk of pulmonary impairment. Although we did not find an association between steroid use before RVI and subsequent pulmonary impairment, we did find an association between lymphopenia at the time of RVI and subsequent pulmonary impairment. Allo-HCT recipients are commonly on immunosuppressive agents, which work by suppressing T lymphocyte function and reducing lymphocyte counts. Immunosuppression in allo-HCT recipients can thereby result in lymphopenia and predispose to more severe infections [49]. Therefore, it is possible that much of the variance in outcome with LRI as a predictor is also explained by the type of conditioning regimen, chronic GVHD, and lymphopenia, but the

Table 3
Competing Risk Model for NRM at 2 Years after RVI with RRM as a Competing Risk

Characteristic	Survivors at 2 Years after RVI (n = 152)	NRM at 2 Years after RVI (n = 30)	Unadjusted		Adjusted	
			SHR for NRM (95% CI)	*P*	SHR for NRM (95% CI)	*P*
Median age at time of RVI,* yr (range)	51 (19-72)	54 (26-77)	**1.4 (1.1-1.8)**	**.02**	**1.4 (1.0-1.8)**	**.03**
Gender, n (%)						
Male	83 (55)	20 (67)	1.0			
Female	69 (45)	10 (33)	.7 (.3-1.4)	.27		
Race,† n (%)						
White	117 (80)	27 (90)	1.0			
Nonwhite	30 (20)	3 (10)	.4 (.1-1.3)	.13		
Underlying malignancy, n (%)						
Acute leukemia	82 (54)	18 (60)	1.0			
Chronic leukemia	28 (18)	2 (2)	.4 (.1-1.8)	.23		
Lymphoma/myeloma	41 (27)	10 (33)	1.1 (.5-2.5)	.71		
Other	1 (1)	0	—	—		
Days between HCT and RVI						
≤100	64 (42)	17 (57)	1.0			
>100	88 (58)	13 (43)	.9 (.6-1.2)	.37		
HCT type, n (%)						
Matched related donor	76 (50)	14 (47)	1.0			
Matched unrelated donor	60 (39)	14 (47)	1.2 (.6-2.5)	.65		
Mismatched	5 (3)	0	—	—		
Haploidentical	4 (3)	0	—	—		
Cord blood	7 (5)	2 (7)	1.2 (.3-5.1)	.83		
Steroids 30 days before RVI, n (%)						
No	83 (55)	5 (17)	1.0		1.0	
Yes	69 (45)	25 (83)	**5.7 (2.2-14.9)**	**<.001**	**5.3 (2.0-13.7)**	**.001**
GVHD prophylaxis, n (%)						
CNI/MTX	131 (86)	27 (90)	1.0	.83		
CNI/MMF	15 (10)	3 (10)	.9 (.3-2.9)			
Other	6 (4)	0	—			
History of acute GVHD before RVI, n (%)						
No	78 (51)	12 (40)	1.0			
Yes	74 (49)	18 (60)	1.6 (.8-3.3)	.20		
History of chronic GVHD before RVI, n (%)						
No	104 (68)	20 (67)	1.0			
Yes	48 (32)	10 (33)	1.2 (.6-2.6)	.65		
Decline in FEV_1 of 10% or greater, n (%)						
No	109 (72)	11 (37)	1.0		1.0	
Yes	43 (28)	19 (63)	**3.9 (1.9-8.1)**	**<.001**	**3.3 (1.6-6.9)**	**.002**
CMV seropositivity,‡ n (%)						
Donor−/recipient−	15 (10)	5 (17)	1.0			
Donor or recipient+	136 (90)	25 (83)	.6 (.2-1.6)	.29		
RVI species, n (%)						
RSV	47 (31)	5 (17)	1.0			
FLU	29 (19)	3 (10)	1.0 (.3-4.4)	.96		
PIV	76 (50)	22 (73)	**2.8 (1.1-7.3)**	**.04**		
Site of infection at time of RVI						
Upper respiratory tract infection	120 (79)	22 (73)	1.0			
LRI	32 (21)	8 (27)	1.2 (.6-2.8)	.60		
Co-infection at time of LRI						
No	128 (84)	24 (80)	1.0			
Yes	24 (16)	6 (20)	1.3 (.5-3.1)	.63		
Anti-viral therapy at time of LRI						
No	62 (41)	14 (47)	1.0			
Yes	90 (59)	16 (53)	.7 (.4-1.5)	.40		
Nonmyeloablative conditioning, n (%)						
No	93 (61)	18 (60)	1.0			
Yes	59 (39)	12 (40)	1.0 (.5-2.0)	.95		
T cell depletion						
No	85 (56)	16 (53)	1.0			
Yes	67 (44)	14 (47)	1.0 (.5-2.1)	.93		
ALC at time of RVI						
$\geq 500 \times 10^6$ cells/L	111 (73)	16 (53)	1.0			
$< 500 \times 10^6$ cells/L	41 (27)	14 (47)	**1.3 (1.0-1.6)**	**.04**		
ANC at time of RVI						
$\geq 500 \times 10^6$ cells/L	146 (96)	28 (93)	1.0			
$< 500 \times 10^6$ cells/L	6 (4)	2 (7)	1.1 (.7-1.8)	.74		

Statistically significant findings are highlighted in bold.
*Analyzed in increments of 10 years.
†Data for race were unavailable for 5 patients.
‡CMV seropositivity data were unavailable for one patient.

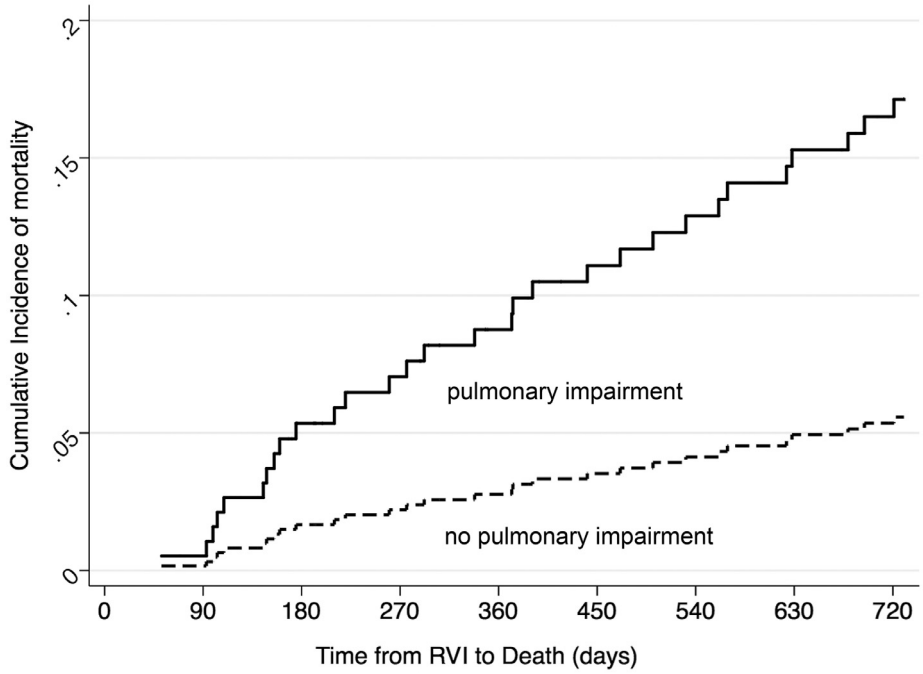

Figure 4. Cumulative incidence function curves for mortality in the first 2 years after RVI among those with pulmonary impairment (*solid line*) and without pulmonary impairment (*dashed line*) after adjustment for age and systemic steroid use within 30 days.

precise contribution of each of these variables to the risk for pulmonary decline needs further study.

To our knowledge this is the first study to show that pulmonary impairment after RVI is strongly associated with increased 2-year NRM in allo-HCT recipients. Development of BOS is associated with increased mortality in allo-HCT recipients [23,28], but allo-HCT recipients with BOS typically have a substantial decline in FEV_1 at the time of clinical evaluation [24,50]. We found that a 10% decline in FEV_1 after RVIs in allo-HCT recipients was a strong predictor for 2-year NRM, suggesting that even small decrements in pulmonary function are associated with worse outcomes after RVI. RVIs induce inflammatory responses in the lung that can injure the airways and lung parenchyma, and these injuries can manifest as declines in FEV_1 [51-53]. In this scenario, impairment in forced spirometry serves as a biomarker for mortality risk in allo-HCT recipients with RVI, analogous to findings in the general population [14-18]. Because most allo-HCT recipients do not die immediately after an RVI episode, these individuals would likely benefit from screening PFTs either administered in a PFT laboratory or through the use of home spirometric monitoring programs [54].

In addition to pulmonary impairment, we found that advanced age and systemic steroid use at the time of RVI were risk factors for 2-year NRM. Advanced age is a well-known marker of adverse outcomes after viral LRI [55] and may be explained in part by the shift from lymphoid to myeloid cell proliferation [56], impaired B and T cell lymphopoiesis [57,58], and impaired T cell co-stimulation [59]. Lymphopenia at the time of RVI is a well-known risk factor for adverse outcomes [3,60], and in a univariate analysis we found that an ALC $< 500 \times 10^6$ cells/L at the time of RVI predicted 2-year NRM. However, in our multivariate competing risk model, increased age predicted 2-year NRM, but an ALC $> 500 \times 10^6$ cells/L did not. Other studies have shown that advanced age and lymphopenia predict mortality in allo-HCT recipients after RSV infection [61] and H_1N_1 influenza infection [12]. Further work is necessary to identify the relative and cumulative impacts of age and lymphopenia on mortality risk in allo-HCT recipients. We also found that systemic steroid use before RVI was a strong predictor of mortality. The immunosuppressive effects of systemic steroids are well known [62], and the primary reason for the use of systemic steroids in our cohort was the treatment of GVHD. In allo-HCT recipients, systemic steroid use in the setting of RVI is associated with increased rates of progression from upper respiratory tract infection to LRI in RSV [63] and PIV infections [64] but not influenza [65,66]. In the general population, however, systemic steroid use during influenza infection has been associated with higher mortality [67]. Both acute and chronic GVHD are associated with increased mortality in proportion to severity [68-70]. Systemic steroid therapy may often be necessary for GVHD treatment, and efforts to minimize immunosuppression must be weighed against the risk of worsening GVHD.

Our study has some strengths and limitations. The strengths included consecutive enrollment of all allo-HCT recipients at a high-volume transplant center, the use of comprehensive infection control, HCT and PFT databases, and complete follow-up of subjects. However, during the study period molecular assays, including multiplex PCR assays, which are sensitive, specific, and comprehensive, were not available at our institution, and therefore we restricted the analysis to allo-HCT recipients with RVI diagnosed by direct immunofluorescent assay or viral culture [71]. In addition, our cohort consisted of allo-HCT recipients who underwent follow-up PFTs to document FEV_1 decline. We may have excluded some patients who did not complete post-RVI PFTs because of debility. This would imply that our cohort could be affected by a survival bias in that patients must be healthy enough to survive to undergo post-RVI PFTs. Because PFTs were not clinically mandated after RVI, an alternative explanation could be that only patients who remained symptomatic underwent post-RVI PFTs, suggesting that these patients had probably persistent postviral inflammation than

did those who did not complete post-RVI PFTs. Similarly, we assumed that pulmonary function remained stable from pre-RVI PFTs to the time RVI. Because pulmonary function tends to decline over time [72], we may have overestimated the decline at the time of RVI in subjects with a long delay between pre-RVI PFTs and time of RVI, which would bias our results toward the null hypothesis. Overall, our cohort is representative of those in typical clinical practice, in which symptomatic patients are evaluated for RVIs, and patients who are able to undergo PFTs after RVI do so. In this representative population, pulmonary impairment was highly predictive of post-RVI NRM. PFTs obtained shortly after RVI may incorrectly identify patients who subsequently recover lung function as "decliners." However, classification of these patients as decliners would bias our results toward the null hypothesis. Furthermore, if PFTs were used to screen for allo-HCT recipients at high risk for NRM after RVI, some false-positive findings may be acceptable to detect all patients at risk for NRM. Few patients in our study developed BOS; therefore, we could not analyze risk factors for post-RVI BOS in allo-HCT recipients. Finally, because of the lack of allo-HCT recipients who had lymphocyte counts below 300×10^6 cells/L, our cut-off for defining lymphopenia (500×10^6 cells/L) was higher than has been used in other studies [12,61], which could overestimate the severity of immunosuppression in allo-HCT recipients we considered to be lymphopenic.

In conclusion, we report that allo-HCT recipients who have pulmonary impairment after RVI are at increased risk for 2-year NRM. Furthermore, increased age and systemic steroid use before RVI were associated with higher 2-year NRM. Increased surveillance with PFTs may identify allo-HCT recipients with early pulmonary impairments after RVI, but the value or benefit of screening will depend on the identification of effective post-RVI interventions to mitigate NRM.

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