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Original Article

Characteristics of community-acquired respiratory viruses infections except seasonal influenza in transplant recipients and non-transplant critically ill patients

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KEYWORDS
Community-acquired respiratory viruses;
Solid organ transplantation;
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Critically ill patients;
Mortality

Abstract *Background/Purpose:* Transplant recipients are vulnerable to life-threatening community-acquired respiratory viruses (CA-RVs) infection (CA-RVI). Even if non-transplant critically ill patients in intensive care unit (ICU) have serious CA-RVI, comparison between these groups remains unclear. We aimed to evaluate clinical characteristics and mortality of CA-RVI except seasonal influenza A/B in transplant recipients and non-transplant critically ill patients in ICU.
Methods: We collected 37,777 CA-RVs multiplex real-time reverse transcription-polymerase chain reaction test results of individuals aged ≥18 years from November 2012 to November 2017. The CA-RVs tests included adenovirus, coronavirus 229E/NL63/OC43, human bocavirus, human metapneumovirus, parainfluenza virus 1/2/3, rhinovirus, and respiratory syncytial virus A/B.
Results: We found 286 CA-RVI cases, including 85 solid organ transplantation recipients (G1), 61 hematopoietic stem cell transplantation recipients (G2), and 140 non-transplant critically ill

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patients in ICU (G3), excluding those with repeated isolation within 30 days. Adenovirus positive rate and infection cases were most prominent in G2 ($p < 0.001$). The median time interval between transplantation and CA-RVI was 30 and 20 months in G1 and G2, respectively. All-cause in-hospital mortality was significantly higher in G3 than in G1 or G2 (51.4% vs. 28.2% or 39.3%, $p = 0.002$, respectively). The mechanical ventilation (MV) was the independent risk factor associated with all-cause in-hospital mortality in all three groups (hazard ratio, 3.37, 95% confidence interval, 2.04—5.56, $p < 0.001$).

Conclusions: This study highlights the importance of CA-RVs diagnosis in transplant recipients even in long-term posttransplant period, and in non-transplant critically ill patients in ICU with MV.

Introduction

The use of effective immunosuppressant (IS) is explored to prevent graft rejection and graft-versus-host disease (GVHD) after solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT). However, immunocompromised conditions induced by IS exacerbate the risk of opportunistic infections.[1–3] Community-acquired respiratory viruses (CA-RVs), as well as multidrug-resistant bacteria and molds, have increasingly become of great importance, comprising a large burden on posttransplant infection.[2–4] CA-RVs can cause lower respiratory tract infection (LRTI), resulting in mortality and life-threatening morbidities in transplant recipients.[5–8] SOT and HSCT recipients face different hurdles, such as susceptibility to CA-RV infection (CA-RVI) within posttransplant timeframe.[1–4,9] HSCT recipients are mainly susceptible to severe CA-RVI in the early posttransplant period, including pre-engraftment with prolonged neutropenia. SOT recipients could be at risk of CA-RVI from the community at any time during the posttransplant period.[1,2,10]

Non-transplant critically ill patients in the intensive care unit (ICU) are another group vulnerable to invasive CA-RVI.[11–15] Among patients with severe rhinovirus pneumonia diagnosed using reverse-transcription polymerase chain reaction (RT-PCR), transplantation did not comprise the majority of underlying conditions (To et al., 78%; Choi et al., 95.4%).[14,15] Most patients with acute respiratory failure by respiratory syncytial virus (RSV) were also not transplant recipients.[16]

Respiratory infections caused by CA-RVs apart from seasonal influenza A/B may have been under-diagnosed before the introduction of multiplex RT-PCR methods.[17,18] As the diagnosis of the precise species of CA-RVI became possible, CA-RVs have had great clinical significance in severely immunocompromised patients.[19] The epidemiology and clinical outcome of adenovirus (AdV), human metapneumovirus (hMPV), parainfluenza (PIV), and RSV in SOT and HSCT recipients have been reported during the past few decades.[4,19] However, there are few reports of unique features and impact on outcome or mortality of CA-RVI in non-transplant critically ill patients in ICU compared to transplant recipients, even though many reports have focused on the comparison of specific CA-RVI, particularly seasonal influenza virus, between SOT and HSCT recipients.[19]

The clinical information of CA-RVI between these susceptible groups will be helpful to clinicians if they need to consider the different strategies or practices for treating CA-RV, especially in severe LRTI cases, among transplant recipients or non-transplant critically ill patients in ICU. This study aimed to evaluate the characteristics and outcome of symptomatic respiratory infection resulting from CA-RVs besides seasonal influenza A/B, between non-transplant critically ill patients admitted to the ICU and transplant recipients.

Methods

Study population and data collection

This was a retrospective cohort study. We retrieved all data regarding 41,489 tests including multiplex RT-PCR and culture for 12 CA-RVs of AdV, coronavirus (CoV) 229E/OC43/NL63, human bocavirus (hBoV), hMPV, PIV 1/2/3, rhinovirus, and RSV A/B, from SOT or HSCT recipients or from non-transplant critically ill patients in ICU who were ≥18 years of age and were admitted between November 2012 and November 2017 at the Severance Hospital, a university-affiliated tertiary-care center in Seoul. We did not include seasonal influenza A/B, which could have been diagnosed using rapid antigen test beside RT-PCR or culture in this study. The CA-RVs tests were performed for patients with a suspicion of symptomatic CA-RVI based on the respective clinician's judgement. We excluded 3426 CA-RVs tests that were performed during the pretransplant period or in recipients who received both SOT and HSCT or re-transplantation. Thereafter, 10,616 and 3794 CA-RVs test results from SOT and HSCT recipients, respectively, were finally included. The non-transplant critically ill patients in ICU had undergone 23,367 CA-RVs tests (Fig. 1). Repeated identical CA-RV isolation in one patient within 30 days were considered as the same infection. Therefore, the cohort included 85 (29.7%) and 61 (21.3%) CA-RVI cases in SOT and HSCT recipients, respectively, and 140 (49.0%) CA-RVI cases in non-

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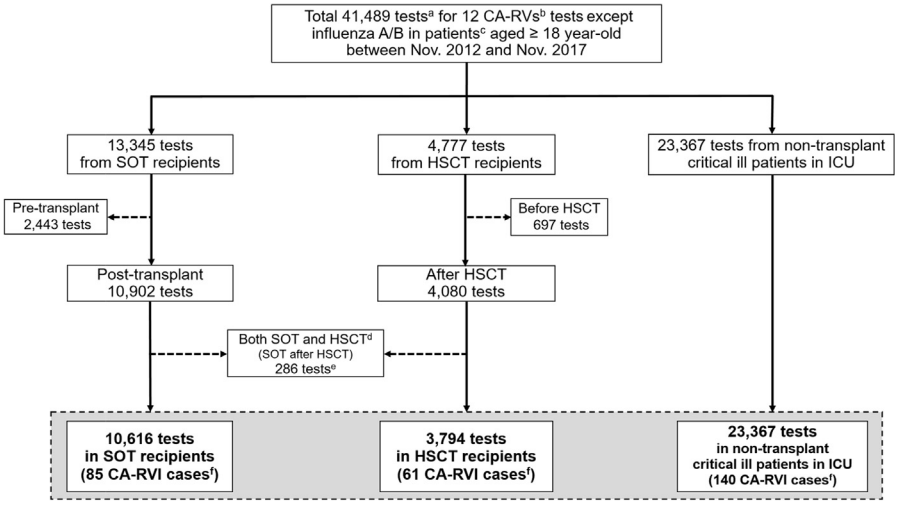

Figure 1. Flow chart of data or case selection for community-acquired respiratory viruses infection except seasonal influenza A/B, [a]The CA-RVs tests included the multiplex RT-PCR or culture, but not antigen or serology tests. [b]The 12 CA-RVs includes adenovirus, coronavirus 229E/NL63/OC43, human bocavirus, human metapneumovirus, parainfluenza virus 1/2/3, rhinovirus and respiratory syncytial virus A/B. [c]SOT, HSCT recipients and non-transplant critically ill patients in ICU. [d]All recipients had received SOT after HSCT (1 liver and 10 lung transplantations). [e]In 286 tests, 5 (1.7%) positive results were 1 of coronavirus OC43, 3 of parainfluenza virus and 1 of rhinovirus. [f]The repeated identical CA-RV isolation in one patient within 30 days were considered as same infection case. All RV cultures were negative, and positive results of CA-RVs were confirmed by multiplex RT-PCR. Abbreviations: CA-RV, community-acquired respiratory virus; CA-RVI, community-acquired respiratory virus infection; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; RT-PCR, reverse transcription-polymerase chain reaction; SOT, solid organ transplantation.

transplant critically ill patients in ICU (Fig. 1 and Table 1). This study was approved by Gangnam Severance Hospital Institutional Review Board, and the need for informed consent was waived due to the retrospective nature of the study.

Detection methods of respiratory viruses

The AdvanSure™ RV multiplex real-time RT-PCR kit with Taqman® probe (AdvanSure; LG Life Sciences, Seoul, South

Table 1 Frequency of community-acquired respiratory virus infection cases except seasonal influenza A/B between SOT recipients, HSCT recipients and non-transplant critically ill patients in ICU.

CA-RVs	Total (n = 286)	Transplant recipients		Non-transplant critically ill patients in ICU (n = 140)	*p*-value
		SOT (n = 85)	HSCT (n = 61)		
Adenovirus	40 (14.0)	10 (11.8)*	14 (23.0)*†	16 (11.4)†	0.039
Bocavirus	5 (1.7)	2 (2.4)	3 (4.9)*	0 (0)*	0.027
Coronavirus	47 (16.4)	16 (18.8)	6 (9.8)	25 (17.9)	0.299
229E	11 (3.8)	6 (7.1)	1 (1.6)	4 (2.9)	0.219
NL63	12 (4.2)	4 (4.7)	3 (4.9)	5 (3.6)	0.797
OC43	24 (8.4)	6 (7.1)	2 (3.3)	16 (11.4)	0.145
hMPV	26 (9.1)	4 (4.7)	4 (6.6)	18 (12.9)	0.090
PIV	50 (17.5)	13 (15.3)	11 (18.0)	26 (18.6)	0.842
PIV1	10 (3.5)	3 (3.5)	1 (1.6)	6 (4.3)	0.775
PIV2	3 (1.0)	0 (0)	1 (1.6)	2 (1.4)	0.597
PIV3	37 (12.9)	10 (11.8)	9 (14.8)	18 (12.9)	0.848
Rhinovirus	85 (29.7)	32 (37.6)*	12 (19.7)*	41 (29.3)	0.042
RSV	33 (11.5)	8 (9.4)	11 (18.0)	14 (10.0)	0.214
RSV A	9 (3.1)	4 (4.7)	2 (3.3)	3 (2.1)	0.552
RSV B	24 (8.4)	4 (4.7)	9 (14.8)	11 (7.9)	0.089

Data are expressed as number (percentage). All cases of community-acquired respiratory virus infection were diagnosed by multiplex RT-PCR. *†Indicate statistically significant difference between two groups using Bonferroni corrected chi-square or Fisher's exact post-hoc tests based on adjusted standardized residuals to control for type I error inflation (adjusted $p < 0.05$). Abbreviations: CA-RV, community-acquired respiratory virus; HSCT, hematopoietic stem cell transplantation; hMPV, human metapneumovirus; ICU, intensive care unit; PIV, parainfluenza virus; RSV, respiratory syncytial virus; RT-PCR, reverse transcription-polymerase chain reaction; SOT, solid organ transplantation.

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Korea) was used to identify 12 CA-RVs of AdV, CoV 229E/OC43/NL63, hBoV, hMPV, PIV 1/2/3, rhinovirus, and RSV A/B from nasopharyngeal aspirate or swab, sputum, bronchoalveolar lavage, and bronchial washing.[20–22] Reverse transcription and amplification steps were automatically conducted on the SLAN-48P/96P systems (Sansure Biotech Inc., Changsha, Hunan Province, PRC, China). The CA-RVs culture was performed through modified shell vial culture.[22]

Definition

The CA-RVs tests have been performed when respiratory infection symptoms such as fever, cough, and sputum were noted, or when the patient was clinically suspected of having a CA-RVI. In some cases, one CA-RV was repeatedly detected at different time points and $\geq$ two CA-RVs were simultaneously detected in one patient. We considered several isolations caused by the same CA-RV within 30 days in one patient as one CA-RVI case. Abnormal findings on chest radiography and/or chest computed tomography (CT) scan was defined as the presence of newly developed lung parenchymal infiltration, as determined by the radiologist. We categorized seasonal variation based on spring (March–May), summer (June–August), autumn (September–November), and winter (December–February).

Statistical analysis

Data were expressed as number (percent) or mean $\pm$ standard deviation or median (interquartile range [IQR]) according to whether they followed the normal distribution or not. Categorical variables were compared using Chi-square test or Fisher's exact test, and post-hoc analysis via Bonferroni correction based on adjusted standardized residuals was used to control for type I error inflation (adjusted p). We used the parametric independent T-test or analysis of variance (ANOVA) test to compare the continuous variables with normal distribution between two or three groups, respectively. Continuous variables without normal distribution between two or three groups were compared using non-parametric Mann–Whitney U test or Kruskal–Wallis test, respectively. The post-hoc tests for continuous variables were performed using Bonferroni correction as a parametric test or Mann-Whitney U test as a non-parametric test ($p < 0.05/3$ [0.0167]). The Kaplan-Meier survival analyses with log-rank test were used to compare all-causes in-hospital mortality. We performed the Cox proportional hazard regression analysis with variables showing statistical significance in univariate analyses to reveal the independent factors in relation to all-causes in-hospital mortality. All two-tailed p-values or adjusted p-values of $\leq$0.05 except post-hoc test using Mann-Whitney U test were considered statistically significant. All statistical analyses and images were performed using SPSS V23 software (IBM Corp., Armonk, NY, USA) and GraphPad Prism V6 (version 6; GraphPad Software, Inc. La Jolla, CA, USA).

Results

Frequency of community-acquired respiratory viruses in laboratory tests and infection cases

Any CA-RVs that were not isolated in culture had been tested in a minority of patients (0.9%). We described the positive rates of all kinds of CA-RVs in multiplex RT-PCR tests that were performed based on clinical suspicion of symptomatic CA-RVI in three different groups (Supplementary Table 1). The positivity of rhinovirus was higher in both SOT and HSCT recipients than in non-transplant critically ill patients in the ICU (3.9% vs. 2.2%, $p = 0.044$). In HSCT recipients, the positive rate of AdV (4.2%) was the most prominent. The positive rates of each CA-RV showed significant differences between three groups for AdV ($p < 0.001$), hBoV ($p < 0.001$), PIV3 ($p = 0.005$), rhinovirus ($p = 0.044$), and RSV A/B ($p = 0.037$). Overall CA-RVs positive rates were the highest in HSCT recipients (0.9% of SOT recipients, 1.7% of HSCT recipients and 0.6% of non-transplant critically ill patients in ICU, $p = 0.034$) (Supplementary Table 1). In the analyses of the total 286 CA-RVI cases, AdV, hBoV, and rhinovirus had significantly different proportions between three groups ($p = 0.039$, 0.027, and 0.042, respectively), with the highest frequency in HSCT recipients for AdV and hBoV or in SOT recipients for rhinovirus. The percentage of AdV infection in HSCT recipients (23.0%) was significantly higher compared to that in SOT recipients (11.8%) or in non-transplant critically ill patients in ICU (11.4%). The HSCT recipients (19.7%) had significantly lower percentages of rhinovirus infection than SOT recipients (37.6%) (Table 1).

Characteristics and outcome of CA-RV infections in three different groups

We analyzed the characteristics of CA-RVI in three groups, and the impact of CA-RVI on the outcome of all-causes in-hospital mortality (Table 2). The most common allograft in CA-RVs-infected SOT recipients was kidney (48.3%), followed by lung (25.3%) and liver (21.8%). In total, 62.3% and 91.8% of CA-RVs-infected HSCT recipients received transplantation from allogeneic donor and stem cell source of peripheral blood, respectively.

The age, male sex, and total duration of hospital stay at the time of CA-RVI were significantly different among the three groups ($p < 0.001$, 0.044 and 0.002, respectively). The non-transplant critically ill patients in ICU were the oldest (68 $\pm$ 14 year-old) and had stayed in hospital during the longest period, with median of 25 days (IQR, 11–45 days). Total duration of ICU stay was not significantly different between non-transplant critically ill patients in ICU and transplant recipients who had ever received ICU (29.4% of SOT and 29.5% of HSCT recipients). The time interval between transplantation and CA-RVI was significantly longer in SOT recipients than in HSCT recipients (30 [10–107] vs. 20 [11–39] months, $p = 0.035$) (Table 2 and Fig. 2). The season of CA-RVI incidence was not different between three groups ($p = 0.206$). The SOT recipients had the significantly lowest all-cause in-hospital mortality (28.2%) among the three groups ($p = 0.002$) (Table 2 and Fig. 3).

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Table 2 Comparisons of clinical characteristics and outcome of community-acquired respiratory viruses[a] infection cases except seasonal influenza A/B in SOT recipients, HSCT recipients and non-transplant critically ill patients in ICU.

Characteristics	Transplant recipients		Non-transplant critically ill patients in ICU (n = 140)	*p*-value
	SOT (n = 85)	HSCT (n = 61)		
Age at CA-RVI, years	56.3 ± 12.1	47.1 ± 15.0	67.8 ± 14.3	<0.001[b]
Sex, male	62 (72.9)*†	34 (55.7)*	81 (57.9)†	0.044
Total hospital stay, days	15 (8–33)	12 (6–36)*	25 (11–45)*	0.002
ICU care				
Yes	25 (29.4)	18 (29.5)	–	>0.999
Duration, days	20 (5-31)[c]	9 (3–35)[c]	8 (4-23)	0.233
Time interval between Tx and CA-RVI, months	30 (10–107)	20 (11–39)	–	0.035
Season				0.206
Spring (n = 97, 34%)	24 (28.2)	23 (37.7)	50 (35.7)	0.420
Summer (n = 55, 19%)	23 (27.1)	9 (14.8)	23 (16.4)	0.084
Autumn (n = 47, 16%)	15 (17.6)	8 (13.1)	24 (17.1)	0.729
Winter (n = 87, 31%)	23 (27.1)	21 (34.4)	43 (30.7)	0.632
Abnormal CXR or chest CT	71 (83.5)	47 (77.0)	115 (82.1)	0.571
Rejection[d] or GVHD[e]	20 (23.5)	19 (31.1)	–	0.346
IVIG therapy	6 (7.1)*	13 (21.3)*†	12 (8.6)†	0.012
Mechanical ventilation	23 (27.1)*	15 (24.6)†	112 (80.0)*†	<0.001
All-cause in-hospital death	24 (28.2)*	24 (39.3)	72 (51.4)*	0.002

[a] Include adenovirus, coronavirus 229E/NL63/OC43, human bocavirus, human metapneumovirus, parainfluenza virus 1/2/3, rhinovirus and respiratory syncytial virus A/B.
[b] Post-hoc *p*-values were all significant between two groups.
[c] Data from transplant recipients who had ever received ICU care.
[d] Include all types (acute/chronic or antibody/cell-mediated) of rejection which were pathologically diagnosed in SOT recipients.
[e] Include acute or chronic GVHD in HSCT recipients. Abbreviations: CA-RV, community-acquired respiratory virus; CA-RVI, community-acquired respiratory virus infection; CT, computed tomography; CXR, chest x-ray; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; IVIG, intravenous immunoglobulin; SOT, solid organ transplantation; Tx, transplantation.
Data are expressed as number (percentage) or mean ± standard deviation or median (interquartile range). *†Indicate statistically significant difference between two groups by post-hoc tests using Bonferroni correction in parametric test ($p < 0.05$) or Mann–Whitney U test in non-parametric test ($p < 0.05/3$ [0.0167]) for continuous variables or by chi-square or Fisher's exact post-hoc tests based on adjusted standardized residuals (adjusted $p < 0.05$) for categorical variables.

Comparison of characteristics between patients who died or not after CA-RV infections

The patients who died in hospital due to any cause of death after CA-RVI were significantly older (62 ± 15 vs. 58 ± 17-year-old, $p = 0.023$) and had significantly higher percentages of administration of intravenous immunoglobulin (20.8% vs. 3.6%, $p < 0.001$) and mechanical ventilation (MV) (78.3% vs. 33.7%, $p < 0.001$) than those who were alive (Table 3). Each CA-RV-infected patient had similar rates for all-cause in-hospital death (AdV, 42.5%; hBoV, 40.0%; CoV, 44.7%; hMPV, 42.3%, PIV 1/2/3, 40.0%; rhinovirus, 38.8%, and RSV A/B, 48.5%).

Independent clinical factors associated with all-causes in-hospital mortality in CA-RVs-infected transplant recipients and non-transplant critically ill patients in the ICU

In the analyses for relation of each CA-RV to all-cause in-hospital mortality, three groups infected by any CA-RV did not show significantly different mortality rate (Supplementary Table 2). In Cox proportional hazard regression model, MV was independent risk factor associated with higher all-cause in-hospital mortality (HR 3.37, 95% CI 2.04–5.56, $p < 0.001$). The transplantation was not independently related to mortality (Table 4).

Discussion

The frequency of each CA-RV except seasonal influenza A/B among the three high-risk groups was heterogeneous despite significant differences in overall frequency, with overall frequency being the highest in HSCT recipients. This study revealed that the proportion of CA-RV species, vulnerable age, and all-cause mortalities in symptomatic CA-RVI were different between SOT and HSCT recipients and non-transplant critically ill patients in ICU group that are populations typically at risk of invasive viral infections. One of our major findings was that AdV caused significantly higher rates of respiratory infection in adult HSCT recipients, as compared to other non-immunocompetent groups. Several studies reported the incidence of, and mortality due to AdV infection in HSCT recipients of

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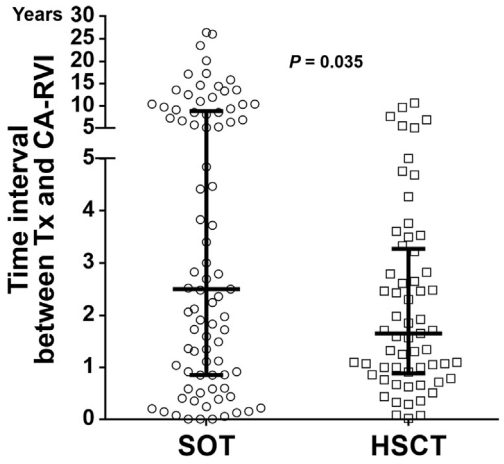

Figure 2. Time intervals between transplantation and community-acquired respiratory viruses[a] infection except seasonal influenza A/B in SOT and HSCT recipients, [a]Include adenovirus, coronavirus 229E/NL63/OC43, human bocavirus, human metapneumovirus, parainfluenza virus 1/2/3, rhinovirus and respiratory syncytial virus A/B. The middle long and upper/lower bars indicate median and upper/lower interquartile values, respectively. Abbreviations: CA-RVI, community-acquired respiratory virus infection; HSCT, hematopoietic stem cell transplantation; SOT, solid organ transplantation; Tx, transplantation.

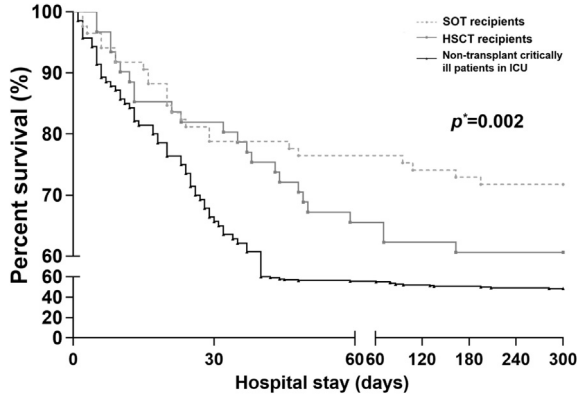

Figure 3. The comparison of all cause in-hospital mortality between SOT recipients, HSCT recipients and non-transplant critically ill patients in ICU with community-acquired respiratory viruses[a] infection except seasonal influenza A/B, *Log rank test (Mantel-Cox). [a]Include adenovirus, coronavirus 229E/NL63/OC43, human bocavirus, human metapneumovirus, parainfluenza virus 1/2/3, rhinovirus and respiratory syncytial virus A/B. Aberrations: CA-RV, community-acquired respiratory virus; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; SOT, solid organ transplantation.

2.7—47% and 4.3—75%, respectively, which were typically higher than SOT recipients, similar to our findings.[4—6,19,23—27] These relatively wide ranges could be due to the characteristics of the study population, including potent conditioning chemotherapy and underlying hematological malignancies, type or repetition of HSCT, era, and occurrence of GVHD.[23,27]

Table 3 Comparison of characteristics between community-acquired respiratory viruses[a]-infected patients[b] who died or not regardless of cause of death.

Characteristics	All-cause in-hospital death		*p*-value
	Yes (n = 120)	No (n = 166)	
Age at CA-RVI, years	62.5 ± 14.7	58.2 ± 16.9	0.023
Sex, male	74 (61.7)	103 (62.0)	>0.999
Species of CA-RV			
Adenovirus	17 (14.2)	23 (13.9)	>0.999
Bocavirus	2 (1.7)	3 (1.8)	>0.999
CoV 229E/NL63/OC43	21 (17.5)	26 (15.7)	0.747
hMPV	11 (9.2)	15 (9.0)	>0.999
PIV 1/2/3	20 (16.7)	30 (18.1)	0.875
Rhinovirus	33 (27.5)	52 (31.3)	0.514
RSV A/B	16 (13.3)	17 (10.2)	0.456
IVIG therapy	25 (20.8)	6 (3.6)	<0.001
Mechanical ventilation	94 (78.3)	56 (33.7)	<0.001

[a] Include adenovirus, bocavirus, coronavirus 229E/NL63/OC43, human metapneumovirus, parainfluenza virus 1/2/3, rhinovirus and respiratory syncytial virus A/B.

[b] Include SOT or HSCT recipients and non-transplant critically ill patients in ICU. Abbreviations: CA-RV, community-acquired respiratory virus; CA-RVI, community-acquired respiratory virus infection; CT, computed tomography; CXR, chest x-ray; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; IVIG, intravenous immunoglobulin; SOT, solid organ transplantation; Tx, transplantation.

Data are expressed as number (percentage) or mean ± standard deviation or median (interquartile range).

In this study, a large proportion of CA-RVs except seasonal influenza resulted in symptomatic respiratory infection at a late posttransplant period, with median of 20 months in HSCT and 30 months in SOT recipients. Like as previous reports,[1,2,4,9,10,28] our data also showed that the posttransplant period in which CA-RVI occurred in SOT recipients was significantly longer than that in HSCT recipients. This finding suggests that physicians need to suspect and diagnosis CA-RVI in transplant recipients with respiratory symptoms regardless of posttransplant period.

Another important finding of this study was that non-transplant critically ill patients in ICU group had high mortality rates after CA-RVI rather than transplant recipients. Our analyses for mortalities showed the MV as traditional risk factor indicating severity of LRTI was independent risk factors for all-causes in-hospital mortality in three immunosuppressive groups with CA-RVI. The species of CA-RV itself independently did not lead to increase mortality. Even though SOT recipients with all kinds of CA-RVI had the lowest mortality rate in the three high-risk groups, we did not find the independent effect of SOT on all-cause mortality in Cox proportional hazard regression model.

Our data showed that hBoV, a recently emerging CA-RV in transplantation,[29] occurred in only five transplant recipients. Although it has been reported that hBoV can cause severe disseminated infections in infants and children recipients,[30,31] the incidence, attributable mortality, and

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Table 4 Factors in relation to all-cause in-hospital mortality in transplant recipients and non-transplant critically ill patients in ICU with community-acquired respiratory virus[a] infection case except seasonal influenza A/B by cox proportional hazard regression analysis.

Variables	All cause in-hospital mortality		
	HR	95% CI	*p*-value
Patient groups			
Non-transplant critically ill patients in ICU	1 (Ref.)	1 (Ref.)	—
SOT recipients	0.87	0.52—1.45	0.587
HSCT recipients	0.61	0.35—1.04	0.169
Older age, ≥ 60-year-old	1.22	0.81—1.84	0.334
IVIG therapy	1.54	0.85—2.49	0.129
Mechanical ventilation	3.37	2.04—5.56	<0.001

[a] Include adenovirus, bocavirus, coronavirus 229E/NL63/OC43, human metapneumovirus, parainfluenza virus 1/2/3, rhinovirus and respiratory syncytial virus A/B. Abbreviations: CA-RV, community-acquired respiratory virus; CI, confidence interval; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; IVIG, intravenous immunoglobulin; Ref., reference; SOT, solid organ transplantation.

effect of hBoV on graft in adult recipients remains unclear.[29] A future multicenter observational study will be helpful to verify the role of hBoV in severely immunocompromised patients.

Even though the CA-RV tests showed the lowest positive rate in non-transplant critically ill patients in ICU group, the frequencies of hMPV and RSV A/B infection associated with detrimental outcomes and treated with specific antiviral agent,[4,5,19,32] in this group were not different compared to transplant recipients. Of 432 non-transplant patients with suspected sepsis in the previous study, 12 (2.8%) had RSV A/B and 23 (5.3%) had hMPV.[33] Gréve et al. reported 7 (0.5%) with hMPV and 21 (1.5%) with RSV among 1407 non-transplant patients admitted to the ICU on MV therapy in a prospective multicenter study in 2018.[11] Recent reports support our findings and indicate that hMPV and RSV should not be regarded as negligible pathogens and could be under-diagnosed in non-transplant critically ill patients, in particular on ventilated and ICU care.[11—13,16,34] However, we do not have any consensus that these CA-RVs are directly related to poor outcome and attributable mortality in this population.[11,12,34] In addition, there is no standard guideline for prevention or treatment of CA-RVs among transplant recipients and non-transplant critically ill patients in ICU. Therefore, the guideline for indication of surveillance or diagnostic tests as well as treatment of specific CA-RVs in unique high-risk subpopulation through further prospective studies needs to be standardized to implement practices effectively.

This study has several limitations; (1) CA-RV tests were performed based on the decisions of individual clinicians and not according to a standard uniform protocol or united prescription criteria. This could have resulted in over-prescriptions leading to the lower positive rate, as well as under-prescriptions as no suspicion of CA-RVI, (2) retrospective data collection precluded us from obtaining precise incidence rates according to year or season. Nevertheless, comprehensive data with nearly total 40,000 exclusively multiplex RT-PCR tests in our study can be seen as a strength. In addition, the data demonstrated that recipients of SOT or HSCT have different frequencies for CA-RVI compared to non-transplant critically ill patients in ICU, and these three high-risk groups with positive rates of each CA-RV in RT-PCR tests were detected on a large scale at one hospital. The data from one hospital might ensure the homogeneity of severity and consistency of laboratory tests in the study population.

In conclusions, non-transplant critically ill patients in ICU group with CA-RVI except seasonal influenza A/B had higher all-cause mortality rate than in transplant recipients. CA-RVI except influenza in transplant recipients could occur in the late posttransplant period of several years. Especially, AdV infection was the most prominent in HSCT recipients. This study suggests the importance of suspicion and diagnosis of CA-RVI in transplant recipients even in the late posttransplant period, and non-transplant critically ill patients in ICU with older age, particularly those with MV.

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Conflicts of interest

None of the authors declares conflicts of interest associated with this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2019.05.007.

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