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Respiratory Viral Infections in Children and Adolescents with Hematological Malignancies

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Abstract. ***Background:*** **Despite the introduction of a polymerase chain reaction (PCR) test for the diagnosis of respiratory viral infection (RVI), guidance on the application of this test and the management of RVI in immunocompromised children is lacking. This study evaluated the clinical characteristics of RVI and established strategies for the PCR test in children and adolescents with hematological malignancies.**

Methods**: This study included children and adolescents with underlying hematological malignancies and respiratory symptoms, in whom a multiplex PCR test was performed. Patients in whom RVI was identified and not identified were categorized into Groups I and II, respectively. Group I was sub-divided into patients with upper and lower respiratory infections. The medical records of the enrolled patients were retrospectively reviewed.**

Results**: A total of 93 respiratory illnesses were included. Group I included 46 (49.5%) cases of RVI, including 31 (67.4%) upper and 15 (32.6%) lower respiratory infections. Rhinovirus (37.0%) was the most common viral pathogen. Significantly more patients in Group I had community-acquired respiratory illnesses (*p*=0.003) and complained of rhinorrhea (*p*<0.001) and sputum (*p*=0.008) than those in Group II. In Group I, significantly more patients with lower respiratory infections had uncontrolled underlying malignancies (*p*=0.038) and received re-induction or palliative chemotherapy (*p*=0.006) than those with upper respiratory infections.**

Conclusions**: A multiplex PCR test should be considered for RVI diagnosis in immunocompromised children and adolescents with respiratory symptoms, especially in those with rhinorrhea or sputum prominent over a cough. The early application of the PCR test in patients with uncontrolled underlying malignancies may improve outcomes.**

Keywords: Child; Hematologic neoplasms; Polymerase chain reaction; Respiratory tract infections.

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Introduction. Infection is the main cause of treatment-related mortality in patients with hematological malignancies.[1] Therefore, the early diagnosis and treatment of infection, as well as infection prevention, are essential to improve the prognosis of immune compromised patients. In these patients, neutropenic fever (NF) has been the focus, and bacterial and fungal infection is emphasized.[2] Among viruses, *Herpesviridae*, which maintains latency and reactivates during immune suppression caused by anti-cancer chemotherapy and hematopoietic cell transplantation (HCT), is considered a major pathogen. However, the causative pathogens are not identified in 53-79% of patients with NF,[3,4] and some of which may be respiratory viruses (RVs).

Viral culture and antigen detection methods have been used for the diagnosis of viral infection. Because these conventional methods have low sensitivity for detecting rhinovirus and enterovirus, which are the most common causes of community-acquired respiratory viral infection (RVI), RVI was identified only in 6-22% of immune compromised children with respiratory symptoms in the past.[5-7] Also, most previous studies were restricted to reporting RVI due to respiratory syncytial virus (RSV), parainfluenza virus, influenza virus, and adenovirus, which could be diagnosed by conventional methods.[8-10] A polymerase chain reaction (PCR) test exhibiting improved sensitivity and specificity in the diagnosis of RVI in immune compromised patients compared to those of conventional methods has been introduced and its use has been extended since the 2000s.[5,6,11] Recent studies using PCR tests identified RVI in 33-76% of children with NF or cancer complaining of respiratory symptoms.[5,6,12-16] RSV and influenza virus were the most frequent causes of RVI in the era of conventional methods,[8-10] whereas rhinovirus was the most frequent cause in the era of PCR tests.[5,6,12-17] In spite of this epidemiological change accompanied by the introduction of PCR tests, reports on the clinical characteristics and prognosis of RVI in immune compromised children and adolescents using PCR tests are lacking. Accordingly, guidelines on the application of a PCR test for the diagnosis and proper management of RVI in immune compromised children and adolescents have not been established.

This study was performed to evaluate the clinical characteristics and outcomes of RVI diagnosed by a multiplex PCR test for RVs and to establish strategies for performing the PCR test in children and adolescents with hematological malignancies, who comprise a major portion of immune compromised children and adolescents.

Patients and Methods. *Patients and study design.* Children and adolescents (<20 years of age) with underlying hematological malignancies treated at the Department of Pediatrics, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, were eligible for this study. Among them, those who complained of respiratory symptoms such as a cough, rhinorrhea, sputum, sore throat, and dyspnea, with or without fever, and in whom a multiplex PCR test for RVs was performed between December 2016 and November 2017 were enrolled. Patients in whom respiratory symptoms developed 6 months or more after the completion of anti-cancer chemotherapy or 2 years or more after HCT were excluded. Patients in whom hematological malignancies were newly diagnosed and anti-cancer chemotherapy had not been administered prior to the development of respiratory illnesses were also excluded. Patients in whom RVs were identified and not identified were categorized into Groups I and II, respectively. The medical records of the enrolled patients were reviewed retrospectively and the clinical and laboratory characteristics were compared between groups. The patients in Group I were sub-divided into those with upper respiratory tract infections (URIs) and lower respiratory tract infections (LRIs) and the clinical and laboratory characteristics were also compared between the two subgroups. This study was approved by the Institutional Review Board of the Seoul St. Mary's hospital with a waiver of informed consent (Approval Number: KC18RESI0302).

Diagnosis and treatment of respiratory viral infections. A nasopharyngeal swab was collected from patients complaining of respiratory symptoms. The samples were sent to the Department of Laboratory Medicine where a multiplex PCR test for RVs was performed using a commercially available kit (AdvanSure™ RV real-time PCR kit, LG Life Sciences Ltd., Seoul, Republic of Korea). The PCR kit tested for influenza A and B viruses, parainfluenza virus, rhinovirus, RSV, human metapneumovirus (HMPV), adenovirus, coronavirus, and human bocavirus. Chest x-ray was routinely performed in patients with respiratory symptoms, and chest computed tomography was performed based on the attending physician's clinical decision. Oseltamivir was administered to all patients diagnosed with influenza. Based on the attending physician's decision, oral ribavirin and intravenous immunoglobulin (IVIG) were administered. Febrile patients received empirical antibiotic therapy.

Definitions. An episode of respiratory illness occurring 4 or more weeks after a previous episode was considered a separate episode if it occurred during a separate admission and the patient did not have respiratory complaints between the two episodes. URI was diagnosed when a patient had respiratory symptoms that were not accompanied by hypoxemia and abnormal findings on chest imaging studies. LRI

was diagnosed when abnormal findings were observed in chest imaging studies. Due to the difficulty associated with obtaining sputum samples and performing bronchoscopy in children and adolescents with underlying hematological malignancies, as they are prone to bleed, nasopharyngeal samples were used to diagnose LRI, although lower respiratory samples are preferred specimens.[18] Community-acquired respiratory illness was defined if respiratory symptoms developed before or within 2 days of admission. Hospital-acquired respiratory illness was defined if respiratory symptoms developed 2 or more days after admission. Neutropenia was defined as an absolute neutrophil count <500/mm^3. Steroid use was defined if any type of glucocorticoids equivalent to 2 mg/kg/day (maximum 20 mg/day) of prednisolone or more were administered for longer than 5 days within 1 month prior to the development of respiratory illness. Oxygen therapy, mechanical ventilator care, intensive care unit admission, and death that occurred within 1 month after the development of respiratory illness were considered complications. Co-infections were defined when any other types of non-viral infection were identified at the same time as the patient complaint of respiratory symptoms. Mortality within 1 month after the development of respiratory illness was determined. Mortality due to RVI was defined when the patient died with persisting respiratory symptoms and signs and no other causes of death were identified.

Statistical analysis. Categorical and continuous factors were compared using a chi-square and Mann-Whitney tests, respectively, for comparisons between the patient groups. Multivariate analyses to identify the independent factors for RVI and LRI were performed for significant factors in univariate analysis using a binary logistic regression analysis. IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses, and statistical significance was defined as a *p*-value <0.05.

Results. During the study period, 74 children and adolescents with underlying hematological malignancies who experienced 93 episodes of respiratory illnesses were enrolled. Nine and five patients each experienced two and three episodes, respectively. The median interval between recurrent episodes of respiratory illnesses was 19 weeks (range, 5-52 weeks). Group I included 46 (49.5%) episodes of RVI, including 31 (67.4%) URIs and 15 (32.6%) LRIs. Eleven (73.3%) of the 15 LRIs were initially diagnosed with URIs that progressed to LRIs. Among the identified RVs, rhinovirus (N=17, 37.0%) was the most frequent (**Table 1**), followed by parainfluenza virus (N=14, 30.4%) and RSV (N=10, 21.7%). In five (10.9%) episodes, two viruses were concurrently identified: two (4.3%) episodes of rhinovirus and parainfluenza virus, two (4.3%) episodes of rhinovirus and RSV, and one (2.2%) episode of RSV and influenza A virus.

Co-infections were identified in 21 (22.6%) episodes. Ten (10.8%) episodes were accompanied by bacteremia (*Escherichia coli* in two, *Pseudomonas aeruginosa* in two, viridans streptococci in two, *Enterococcus faecium* in two, *Streptococcus pneumoniae* in one, and *Staphylococcus epidermidis* in one). Eight (8.6%) episodes were accompanied by invasive pulmonary aspergillosis, and two (2.2%) episodes were accompanied by herpetic gingivostomatitis. Chickenpox, *Pneumocystis jirovecii* pneumonia, and *Clostridium difficile* infection accompanied one (1.1%) episode each.

The rate of RV positivity was highest in autumn; however, no significant differences were found among the four seasons (range, 31.6-61.5%, *p*=0.258). Seven RSV infections occurred within a one-month interval in the same ward, six (85.7%) of which were hospital-acquired infection.

Comparison between Group I and Group II. The rates of different underlying hematological malignancies and administered chemotherapies preceding respiratory illnesses were not significantly different between the two groups. Significantly more patients in Group II

Table 1. Distribution of respiratory viruses.

Virus	Total (N=46)	URI (N=31)	LRI (N=15)	*p* value
Rhinovirus	17 (37.0)	15 (48.4)	2 (13.3)	0.021
Parainfluenza virus	14 (30.4)	10 (32.3)	4 (26.7)	1.000
Respiratory syncytial virus	10 (21.7)	5 (16.1)	5 (33.3)	0.257
Coronavirus	4 (8.7)	3 (9.7)	1 (6.7)	1.000
Human metapneumovirus	3 (6.5)	1 (3.2)	2 (13.3)	0.244
Adenovirus	2 (4.3)	1 (3.2)	1 (6.7)	1.000
Influenza A virus	1 (2.2)	1 (3.2)	0 (0.0)	1.000
Influenza B virus	0 (0.0)	0 (0.0)	0 (0.0)	NA
Human bocavirus	0 (0.0)	0 (0.0)	0 (0.0)	NA

Data are numbers (%). LRI=Lower respiratory tract infection, NA=Not available, URI=Upper respiratory tract infection.

Table 2. Comparisons of characteristics between Groups I and II.

Factor	Group I (N=46)	Group II (N=47)	*p* value
Sex, male	26 (56.5)	26 (55.3)	0.907
Age, yr, median (range)	6 (1-19)	12 (0-18)	0.137
Hospital-acquired respiratory illness	16 (34.8)	31 (66.0)	0.003
Underlying hematological malignancy			0.333
Acute lymphoblastic leukemia	29 (63.0)	26 (55.3)	
Acute myeloid leukemia	15 (32.6)	13 (27.7)	
Non-Hodgkin lymphoma	2 (4.3)	5 (10.6)	
Juvenile myelomonocytic leukemia	0 (0.0)	2 (4.3)	
Mixed phenotype acute leukemia	0 (0.0)	1 (2.1)	
Complete remission/response state	32 (69.6)	32 (68.1)	0.878
Steroid use within prior 1 month	29 (63.0)	25 (53.2)	0.336
Neutropenia on the development of respiratory illness	16 (34.8)	27 (57.4)	0.028
Accompanying respiratory symptom			
Fever	41 (89.1)	41 (87.2)	0.777
Cough	35 (76.1)	29 (61.7)	0.134
Rhinorrhea	32 (69.6)	12 (25.5)	<0.001
Sputum	23 (50.0)	11 (23.4)	0.008
Dyspnea	6 (13.0)	11 (23.4)	0.196
Sore throat	6 (13.0)	6 (12.8)	0.968
Complication			
Oxygen therapy	7 (15.2)	14 (29.8)	0.093
Ventilator care	0 (0.0)	8 (17.0)	0.006
Intensive care unit admission	1 (2.2)	11 (23.4)	0.002
Death	2 (4.3)	4 (8.5)	0.677
Co-infection	7 (15.2)	14 (29.8)	0.093
Invasive pulmonary aspergillosis	4 (8.7)	4 (8.5)	
E. coli bacteremia	0 (0.0)	2 (4.3)	
P. aeruginosa bacteremia	0 (0.0)	2 (4.3)	
Viridans streptococcal bacteremia	0 (0.0)	2 (4.3)	
E. faecium bacteremia	0 (0.0)	2 (4.3)	
Herpetic gingivostomatitis	0 (0.0)	2 (4.3)	
S. epidermidis bacteremia	1 (2.2)	0 (0.0)	
S. pneumoniae bacteremia	0 (0.0)	1 (2.1)	
P. jirovecii pneumonia	0 (0.0)	1 (2.1)	
C. difficile infection	1 (2.2)	0 (0.0)	
Chickenpox	1 (2.2)	0 (0.0)	

Data are numbers (%).

presented with hospital-acquired respiratory illnesses (p=0.003), and accompanied neutropenia (p=0.028) than those in Group I (**Table 2**). Most patients overall complained of fever and cough; however, those in Group I complained of rhinorrhea (p<0.001) and sputum (p=0.008) more frequently than those in Group II. In multivariate analysis, rhinorrhea, sputum, and community-acquired respiratory illness were significant factors for a diagnosis of RVI (**Table 3**). Significantly more complications occurred in patients in Group II compared to those in Group I (**Table 2**). Mortality was higher in Group II than that in Group I; however, the difference was not statistically significant.

Comparison between patients with upper and lower respiratory tract infections. In the patients in Group I, those with LRIs were more likely to have uncontrolled underlying malignancies (p=0.038) and receive re-induction or palliative chemotherapy (p=0.006) than those with URIs (**Table 4**). Among respiratory symptoms, sputum (p=0.028) and dyspnea (p=0.001) were more frequently accompanied by LRIs. More patients with LRIs experienced co-infections than those with URIs (p=0.029). Among the five patients with LRIs and co-infections, four experienced invasive pulmonary aspergillosis: two of whom had concomitant RSV infection, another had concomitant adenovirus infection, and the other had HMPV infection. The other experienced *C. difficile* infection with concomitant parainfluenza virus infection. The two patients with URIs and co-infections experienced chickenpox with concomitant rhinovirus infection, and *S. epidermidis* bacteremia with concomitant RSV infection, respectively. The rate of rhinovirus infection was significantly higher in patients with URIs than in those with LRIs (p=0.021). Other viral infections showed no significant association with LRIs (**Table 1**). There were no independent risk factors for LRI in multivariate analysis (data are not shown). Of 14

Table 3. Multivariate analysis to determine the independent factors for respiratory viral infection.

Factor	Odds ratio	95% confidence interval	*p* value
Hospital-acquired respiratory illness	0.320	0.115-0.888	0.029
Neutropenia	0.792	0.286-2.198	0.655
Rhinorrhea	4.902	1.843-13.036	0.001
Sputum	3.026	1.079-8.489	0.035

Table 4. Comparisons of characteristics between children with upper and lower respiratory tract infection.

Factor	With URIs (N=31)	With LRIs (N=15)	*p* value
Sex, male	17 (54.8)	9 (60.0)	0.741
Age, yr, median (range)	6 (1-18)	7 (3-19)	0.110
Hospital-acquired respiratory tract infection	8 (25.8)	8 (53.3)	0.066
Underlying malignancy			0.089
Acute lymphoblastic leukemia	22 (71.0)	7 (46.7)	
Acute myeloid leukemia	7 (22.6)	8 (53.3)	
Non-Hodgkin lymphoma	2 (6.5)	0 (0.0))	
Complete remission/response state	25 (80.6)	7 (46.7)	0.038
Chemotherapy preceding respiratory tract infection			0.006
Induction chemotherapy	2 (6.5)	0 (0.0)	
Re-induction chemotherapy	2 (6.5)	4 (26.7)	
Consolidation chemotherapy	11 (35.5)	1 (6.7)	
Maintenance chemotherapy	10 (32.3)	3 (20.0)	
Palliative chemotherapy	0 (0.0)	4 (26.7)	
Allogeneic hematopoietic cell transplantation	6 (19.4)	3 (20.0)	
Steroid use within prior 1 month	19 (61.3)	10 (66.7)	0.723
Neutropenia on the development of RVI	9 (29.0)	7 (46.7)	0.239
Accompanying respiratory symptom			
Fever	28 (90.3)	13 (86.7)	1.000
Cough	21 (67.7)	14 (93.3)	0.074
Rhinorrhea	23 (74.2)	9 (60.0)	0.495
Sputum	12 (38.7)	11 (73.3)	0.028
Sore throat	6 (19.4)	0 (0.0)	0.157
Dyspnea	0 (0.0)	6 (40.0)	0.001
Complication			
Oxygen therapy	0 (0.0)	7 (46.7)	<0.001
Intensive care unit admission	0 (0.0)	1 (6.7)	0.326
Death	0 (0.0)	2 (13.3)	0.101
Co-infection	2 (6.5)	5 (33.3)	0.029
Oral ribavirin treatment	5 (16.1)	8 (53.3)	0.014
Intravenous immunoglobulin treatment	2 (6.5)	4 (26.7)	0.078
White blood cell count, /mm^3, median (range)	2,100 (130-14,680)	2,190 (40-19,000)	0.806
ANC, /mm^3, median (range)	1,610 (0-8,808)	742 (0-13,680)	0.752
ALC, /mm^3, median (range)	394 (62-5,432)	504 (0-5,164)	0.292
AMC, /mm^3, median (range)	272 (0-2,129)	130 (0-2,382)	0.665
ESR, mm/hr, median (range)	8 (2-54)	10 (2-120)	0.344
C-reactive protein, mg/dL, median (range)	1.31 (0.02-12.58)	3.74 (0.27-25.33)	0.030

Data are numbers (%). ALC=Absolute lymphocyte count, AMC=Absolute monocyte count, ANC=Absolute neutrophil count, ESR=Erythrocyte sedimentation rate, LRI=Lower respiratory tract infection, RVI=Respiratory viral infection, URI=Upper respiratory tract infection.

patients with parainfluenza virus infection, five (35.7%) received ribavirin treatment and one (7.1%) also received IVIG. Of 10 patients with RSV infections, eight (80.0%) received ribavirin treatment and three (30.0%) also received IVIG. Patients with LRIs were more likely to receive oxygen therapy (p<0.001) than those with URIs and mortality was higher in patients with LRIs compared to those with URIs, although the difference was not statistically significant (p=0.101). All of the fatalities in both groups were caused by uncontrolled underlying malignancies.

Discussion. In this study, the clinical characteristics

and outcomes of RVI were investigated in children and adolescents with hematological malignancies. RVI was diagnosed in about half of the enrolled patients, consistent with the results of previous studies using PCR tests to diagnose RVI.[5,12-15] Rhinovirus rather than RSV and parainfluenza virus was the most frequent cause of RVI, consistent with the results of recent studies using PCR tests.[5,6,12-16] RVI investigation should be considered in immune compromised patients complaining of community-acquired respiratory symptoms, preferably in those with rhinorrhea or sputum predominant over a cough. If we consider that early termination of empirical antibiotic therapy led to a favorable outcome in children and adolescents with NF and RVI in a recent report by Santolaya et al,[15] early diagnosis of RVI by a PCR test in these patients can help to avoid an unnecessary antibiotic use.

Neutropenia was identified in only 34.8% of the patients diagnosed with RVI in this study. Therefore, the diagnosis of RVI should not be restricted to patients with NF. As a matter of fact, patients in Group II, in whom the presence of RVs was not identified, were more likely to have neutropenia, hospital-acquired and severe respiratory illnesses, and infections with non-viral pathogens. This suggests that patients in Group II underwent more aggressive anti-cancer chemotherapies, had a more severe immunosuppression, and were hospitalized for longer periods, compared to patients in Group I. Thus, pulmonary edema arising from hyper-hydration during anti-cancer chemotherapy, pulmonary hemorrhage due to thrombocytopenia, and bacterial and fungal pneumonias could lead to respiratory symptoms in these patients. A negative PCR result in patients with NF and hospital-acquired respiratory illnesses may suggest the presence of more severe infection or treatment-related complications.

Although community-onset respiratory illness was significantly associated with the diagnosis of RVI in this study, 13-80% of RVI cases were hospital-acquired infection in several studies, [6-9,19] including the present study (34.8%). Outbreaks of RSV and parainfluenza virus infection have been reported in an outpatient department as well as in an inpatient ward;[20-22] we also experienced an outbreak of RSV infection in seven patients in one month in a closed hematology ward. Therefore, a multiplex PCR test for RVs should be encouraged even in hospitalized patients complaining of rhinorrhea or sputum, particularly when other patients with RVI are hospitalized in the same ward or there is an RVI epidemic in the community. A timely application of the PCR test can lead early diagnosis of RVI in hospitalized patients, and to a subsequent decrease in the RVI transmission within the hospital environment.

Recent studies on RVI in immune compromised children showed low mortality due to RVI, 0-3%.[5,2-16,19] Fortunately, there was no death due to RVI in this study. This favorable outcome may be attributed to a growing concern for RVI in physicians, increasing diagnostic rates especially of mild RVI cases using PCR tests, and improved supportive care in immune compromised patients. Ribavirin-based anti-viral therapy can reduce progression from URI to LRI and mortality in RSV-infected HCT recipients;[23] however, it is not recommended in patients with hematological malignancies who are not receiving HCT and its effect on parainfluenza virus infection has not been confirmed.[24] In this study, 80.0% of patients diagnosed with RSV infection received ribavirin-based anti-viral therapy, regardless of receiving HCT, and none of them died due to RSV infection. However, the efficacy of the ribavirin-based therapy should be further evaluated as the anti-viral therapy performed in this study did not rely on currently established criteria.

The risk factors for mortality due to RVI could not be determined in this study because there were no deaths attributable to RVI. Most previous studies universally reported that LRI is associated with the increased mortality.[7,10,19,23,25-27] Even in rhinovirus infection, which causes milder respiratory illnesses compared to those of RSV, parainfluenza virus and influenza virus, mortality was significantly higher in patients with LRIs than that in those with URIs.[26] Therefore, the early detection of patients at risk of progression to LRIs and early application of proper management for LRIs are necessary to improve the outcome of RVI in immune compromised patients. Low absolute lymphocyte, neutrophil, and monocyte counts; relapsed underlying malignancies; unrelated or mismatched allogeneic-HCT; recent steroid use; oxygen need; and co-infections are risk factors for LRI or mortality.[9,10,23,25-27] These risk factors represent the severity of immune suppression in the infected hosts.[9,25] Accordingly, an immunodeficiency scoring system to predict outcomes and determine the administration of anti-viral therapy has been applied to RSV-infected HCT recipients.[28] The uncontrolled state of underlying hematological malignancies and the presence of co-infections were significantly associated with the development of LRI in this study, which underscores the importance of the host's overall immune status in the outcome of RVI. As a result, a multiplex PCR test for RVs should be performed preferentially in patients complaining of rhinorrhea or sputum and with relapsed or refractory underlying hematological malignancies, co-infections, or severe cytopenia. Considering that 73.3% of LRI cases progressed from URIs in this study, the early application of a multiplex PCR test during the URI period should be emphasized.

This study had some limitations, including biases arising from its retrospective study design. The number of enrolled patients may not be appropriate, and we

lacked a control group including patients without respiratory symptoms. Although lower respiratory samples, such as sputum and bronchial washing or bronchoalveolar lavage fluids, are preferred samples for LRI diagnosis, upper respiratory samples were used in this study. To assure an improved diagnosis of LRI, abnormal findings in chest imaging studies were mandatory for LRI diagnosis in this study; however, lower respiratory samples could reveal clearer pathogenic profiles. The seasonal distribution and epidemics of RVI in immune compromised patients are correlated with those observed in the community.[8,29] During the study period, the epidemics of RSV and influenza virus infection in the community were not prominent in Korea compared to previous years. The inclusion of more RSV and influenza virus infection episodes may modify the outcome of RVI in this study. Future studies should analyze data gathered for several years to include more cases of RVI caused by a variety of RVs. A multiplex PCR test for RVs was not routinely performed in children and adolescents with respiratory symptoms in our hospital during the study period and was hardly performed in the outpatient clinic. Therefore, children and adolescents with mild respiratory symptoms and URIs could not be included in this study. The outcomes of RVI in immune compromised children and adolescents may be more favorable with the inclusion of mild RVI cases.

Conclusions. Considering the confirmed RVI diagnosis in half of the immune compromised children and adolescents with respiratory symptoms in this study, the introduction of multiplex PCR tests for RV detection in this population should be encouraged, especially for patients complaining of rhinorrhea or sputum prominent over a cough. Moreover, the PCR test should address patients with more severe immune suppression, e.g., those with relapsed or refractory underlying malignancies and co-infections, as they are prone to have severe RVI-related outcomes. In addition, infection control strategies to prevent RVI transmission within the hospital environment should be emphasized, considering the current scenario, in which effective anti-viral therapies have not been established for most RVI cases. Thus, early RVI detection by a PCR test may open a window of opportunity for early intervention and infection control.

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